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Table of Contents

AGRANULOCYTOSIS.[1]

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THE study of the rare syndrome first described as "agranulocytic angina" is of great interest. Not only is the condition important on account of its high mortality, but its recognition and investigation have emphasized several important facts concerning the life and function of the neutrophile polymorph leucocyte.

In this paper I have made no attempt to present a series of cases as such; the difficulty in collecting a series is seen in the work of Jackson, Parker and Taylor,[(1)] whose sixty-nine patients were treated by forty different physicians in twelve States of the United States of America. I have rather tried to present a general account of the subject, using case records to illustrate interesting points.

The word "agranulocytosis" is one of the minor horrors of nomenclature, for its construction would imply that it means a state in which the non-granular cells of the blood are increased, whereas it is used for the condition in which the granular cells tend to disappear. However, like "uræmia" and "vitamin", it has probably come to stay. The terms "granulopenia" or "granulocytopenia" and "neutropenia" are preferable for that state of the blood in which the granular leucocytes are reduced in number; and when used with some prefix, such as "malignant", they aptly describe the fully developed and highly lethal syndrome of agranulocytosis. This may be defined as a condition in which the granular leucocytes tend to disappear more or less completely from the circulating blood, with

[1] Read at a meeting of the Section of Medicine of the New South Wales Branch of the British Medical Association on June 13, 1935.

practically no alteration of the other cellular elements; in which there is very frequently a severe inflammatory and necrotic reaction of certain mucous membranes, particularly the throat; and in which there is a most intense systemic disturbance, resulting in a high mortality. This curious specificity of the blood changes is its essential feature, which is interesting, inasmuch as the red cells and platelets are virtually unchanged. It appears from clinical and pathological studies in this disease that the presence of granulocytes in the circulating blood is absolutely necessary for life. In fact, once they have disappeared it would appear impossible for a man to live a week unless restitution of the lacking cells takes place.

Not all forms of granulopenia are so dramatic as the acute type referred to here; there are more chronic and relapsing forms, which will be described later. Some of the more chronic types may not be actually dangerous, but they are potentially so, for the reserve of granular cells is probably slight in these cases.

The syndrome is rare, but, judging by the literature, it is becoming more frequent. This may be due to wider recognition of its features or to increasing use of amidopyrine, known to be a cause. Plum[2] has recently collected 128 cases reported since May, 1933, following the administration of amidopyrine; of these, 68 were reported in the American literature, and most of the remainder came from northern Europe. The same writer, in a previous communication, collected 41 cases occurring in Denmark alone. Adams,[31] in his report for the British Ministry of Health, just to hand, quotes the figures of Kracke and Parker for the period 1922-1932. Up to 1932 there were well over one thousand cases in the world literature, of which 473 were from the United States of America, 350 from Germany, and 100 from France, but only 22 from Britain. Surely more cases have actually occurred in Britain, even allowing for possible diagnostic errors in some of the cases from other countries. The question arises now as to whether we should have seen more cases in Australia. It is striking that in the Royal Prince Alfred, Saint Vincent's and Prince Henry Hospitals in Sydney, and the Royal Melbourne and Alfred Hospitals in Melbourne, there have not been more than seven cases of agranulocytosis found on searching the records of these institutions over a period of several years. In all, I have knowledge, mainly second-hand, of at least twelve cases, but I feel that these figures do not represent the true incidence of the disease. Some cases are possibly wrongly filed in hospital records, but surely some still pass unrecognized. So far as I know, only three cases have actually been reported in the Australian literature; it is time that more publicity was given to this subject.

As recognition of the syndrome depends upon accurate examination of the blood, it is as well to consider some of the principles that underlie supply of leucocytes to the blood stream. It must be remembered that the normal variation in the white cell count, even in the same individual, is considerable. Sabin[3] and others demonstrated that there was a definite rhythm of the white blood cells, with an interval of about an hour's duration; that the numbers of neutrophile cells increased in the afternoon independently of the rise known to occur after food; that the total number might show up to 100% variation; and that the neutrophile cells die out in showers, being promptly replaced by similar showers from reserves, which are probably held in the bone marrow. Stetson[4] and others have also shown that there are considerable fluctuations in the normal white cell count from day to day. These facts should be borne in mind in assessing the information given by blood counts in all cases.

A point that is of great importance in the present instance is the viability of the granulocyte. Its life span is believed to be from three to five days; after this period it is broken down in the blood stream, apparently, and in part is eliminated by the mucosal surfaces. It matures from the parent cell by a process of development that may be traced through its stages in the bone marrow, and has been noted in the blood in myeloid leuchæmia after transfusion. It would appear that the time occupied by this process of maturation is about three to seven days, most of this time being taken up by the changing of the premyelocyte into the metamyelocyte. The latter can become the adult granulocyte very quickly; evidence points to this stage being accomplished in a matter of hours or even minutes. Thus it will be seen that if all production ceases the granulocytes dwindle as soon as the reserves fail; these are probably considerable in extent, for the bone marrow is a huge organ. Its granulopoietic portion has been estimated as being nine and a half to twelve times the volume of the spleen, and is larger than the erythropoietic part, owing to the greater fragility and lability of the cells it produces. But if maturation fails, the whole supply will be exhausted certainly in several days. It has been suggested that to beckon the metamyelocytes into the blood stream needs merely a chemotactic factor, which appears to arise from by-products of broken-down granulocytes. This seems likely, but of even greater importance is the concept of a maturation factor which is essential in order to complete the development of the stem cells. It is conceivable that these two may be different factors, for though a great emergency could be quickly dealt with by summoning up the waiting metamyelocytes and pouring them into the blood current, maturation requires thought in advance, as it were, for the needs of the body cannot be met until the necessary period of several days has passed, unless indeed the process can be specially hurried under conditions of dire stress. On the analogy of the red cells and our knowledge of the pathology of pernicious anæmia it would appear a perfectly justifiable assumption to postulate this factor necessary to mature the stem granulocyte in the marrow. Recent work of Miller and Rhoads[5] is enlightening. These workers have studied "black tongue" in dogs, a

disease apparently homologous with pellagra in man, and they found that prolonged feeding of their dogs with a diet poor in the vitamin *B* complex could cause an acute febrile disorder with stomatitis, granulopenia and characteristic lesions in the bone marrow. In these experimental animals there was apparently some arrest of the maturation of the granulocytes, though this was never complete; nevertheless some animals died, and the lesions in the marrow certainly bear a very strong resemblance to those seen in human patients dying of agranulocytosis. Is there then some chemical dietary deficiency which may be responsible for the arrest, partial or total, of the maturation of the granular leucocytes? Future work may well be directed along these lines.

It may also be possible that under certain conditions, for example, in agranulocytosis and leuchæmia, the leucocytes put out into the blood stream may be of poor quality and may thus perish quickly. Rutledge and others,[6] using vital methods of staining, made studies of the viability of the granulocytes in a patient who suffered from recurrent neutropenia and found that the life of these cells was reduced. If this is so, then there may be an exaggeration of the normal rhythm observed by Sabin and others; the "showers" of dying leucocytes might thus greatly increase in numbers, making great demands on the marrow. It seems possible that the granulocyte may have a much shorter life than its alleged three to five days; even in the normal person it is quite possible that this may sometimes be so. It would also follow that alterations in the rhythm of its life could reflect on the immunity state of the individual, for the polymorph leucocyte is thought to produce complement and perhaps other immune bodies also.

It may here be remarked that there is evidence in the human subject that there is a latent period that elapses before the more primitive cells in the marrow are available in the blood stream after a temporary hold-up in development. In cases of agranulocytosis where treatment has apparently been successful in stimulating the laggard marrow cells, the time taken to produce this response is as a rule several days. This corresponds with the theoretical period expected.

Symptoms.

The literature contains abundant descriptions of the striking clinical syndrome we are considering. These may be briefly summarized.

The Acute Form.

Many of the patients suffering from the acute form have been ailing in some way or other prior to the onset. Either they have been suffering from some debilitating disease for which they have taken drugs, particularly certain analgesics, or they have complained of fatigue, drowsiness and lack of vitality. A previous history of mental stress is not infrequent. The patients are more often women than men, in the ratio of 3 or 4 to 1, in some series; they are usually of middle age, or even older. Prostration is a constant, early and striking feature; the patient feels very ill, is febrile, has shivers or definite rigors, and may become jaundiced. Itching of the skin has been noted very early by some observers. In its most intense form the disease is a fulminating illness, dramatic and soon obviously likely to threaten life. The mucous lesions excited the attention of the earlier writers on the subject, but though they are of evident significance in diagnosis and prognosis, it is now agreed that they are a secondary part of the picture only. Sore throat is extremely common; there is a concomitant dysphagia, due to the ulcerative and necrotic lesions seen in the mouth and fauces. Any of the vulnerable mucosæ may be attacked; ulcers have been demonstrated *post mortem* in all parts of the alimentary tract, and the vagina and cervix are sometimes attacked also. Skin surfaces may suffer also. It is worthy of note that in two cases recorded in the local literature this was found; Dr. Maisie Asher's patient[7] showed an umbilical lesion, and Dr. Wigg's patient[8] an inflammation in the neighbourhood of the anus. The organisms found in the necrotic ulcers are many, but the most characteristic are the fuso-spirochæte of Vincent. An interesting point is the condition of the lymph nodes. It might be thought that the blow struck at the patient's immune mechanism is so overwhelming that lymph gland swelling would not occur, but it must be remembered that these glands are concerned rather with the lymphocytes than with the granular white cells. Thus it is found that there is frequently some swelling of the drainage glands, especially in the less fulminating cases, and slight enlargement of the spleen is sometimes also found. After an intense illness lating a few days only the patient may succumb, or he may die after several weeks, sometimes even after an attempt to remedy the essential blood defect has been made by the bone marrow. Signs of pneumonia are sometimes observed, either of bronchial or lobar type. This is important, for the true nature of the illness might be overlooked. As originally pointed out by Schultz in 1922, pneumonia is a common terminal event. An illustrative case is as follows:

CASE I.—A man, aged sixty years, had complained of some general abdominal pain for three weeks and a cough for ten days. For two days before admission to hospital he had troublesome pain in the abdomen and vomiting. He had no sore throat. Fever was present and there was great prostration. Friction sounds were heard in one axilla, and moist râles at the lung bases. Blood examination revealed 4,100,000 red cells per cubic millimetre, but only 800 white cells, of which 80% were lymphocytes and 20% monocytes. No granular leucocytes were seen. Though no definitely necrotic lesion was found in the throat, swabbing revealed a few spirochætes and fusiform bacilli. He died after a brief illness of five days, during which there was no regeneration of the white cells in the blood. Autopsy showed no definite anomaly in any organ except the lungs, where a hæmorrhagic thickening was found at one base, resembling the consolidation of a pneumonia.

The essential feature of the syndrome is the disappearance of the granulocytes from the circulating blood. These cells may vanish completely or may be

present in very small numbers; primitive leucocytes are not seen. The total white cell count is usually very considerably reduced, especially in the latter stages, but in rare cases there has been found an increase of other cells, for example, the monocytes. The absolutely characteristic picture is that of a blood approximately normal except for the general lowering of the white cells and the absence of granular leucocytes. The red cells and platelets are virtually unaffected; this is a most important diagnostic finding, for if there are substantial alterations in the red cells or platelets, they are no part of the essential syndrome of agranulocytosis. It may, of course, happen that granulopenia occurs in a person who is already the subject of an anæmia of secondary type. Relapse is not very infrequent, and in this case the rising numbers of granular cells dwindle again and the cycle is repeated. It is of interest that death may occur, even though the leucocytes are returning to the blood. An example of this is seen in the following case.

CASE II.—A woman, aged thirty-three years, had been treated by a non-medical man for pains in the limbs; the possible importance of this will be noted in view of the position occupied by amidopyrine in the ætiology. It was not discovered, however, just what treatment had been given. Her last menstrual period ended two days prior to her admission to hospital—another possibly significant fact. One week before her admission to hospital she had been seized with a febrile illness, with headache, diarrhœa and delirium; she felt very ill and complained of a sore throat. On admission the tonsils were sloughy and bleeding, and swabbing revealed fusiform bacilli and spirochætes. There were some subcutaneous hæmorrhages on the fingers and elbows, and blood was vomited and passed *per rectum*. One injection of "Novarsenobillon" was given, and two whole blood transfusions, but after eight days in hospital she died.

The blood on her admission to hospital showed 3,280,000 red cells and 700 white cells per cubic millimetre, and only 20% of the total leucocytes were neutrophile cells. Later the white cell count rose to 3,000 per cubic millimetre, with 60% neutrophile cells, and then to 6,520 (83% neutrophile cells), and following the transfusions the total leucocytes were 6,280, with 63% neutrophile cells.

It might have been thought that the normal count was a good prognostic, but this is not always so, and the patient died in spite of the restitution of the normal blood picture.

This patient had some degree of red cell deficiency, but there was no evident anomaly of the erythrocytes, and this does not invalidate the diagnosis.

Subacute Types.

The less acute forms are less dramatic. Usually some septic or debilitating infective state brings the patient under observation and it is found that the intensity of the symptoms, particularly those of fatigue and malaise, are much in excess of what might be expected on ordinary clinical grounds. There can be no doubt that more of these cases will be recognized now that clinicians are on the lookout for them. The importance of this subacute or chronic granulopenia is well illustrated by the following case, quoted by courtesy of Dr. O. A. A. Diethelm.

CASE III.—A woman, aged fifty-seven years, was a sufferer from functional dyspepsia and was found to have septic tonsils. When she came under observation her red cells numbered 3,740,000 and the white cells only 1,800, of which only 2% were neutrophile cells. The danger of her condition was recognized, and she was given general and special hæmatinic treatment for a time, her white cell count rising from below 2,000 to 3,000 per cubic millimetre, the neutrophile cells increasing from 20% to 45%. The tonsils were dealt with by diathermy, the leucocytes rising to 5,000, with 57% neutrophile cells.

This patient did not actually suffer from a severe agranulocytosis, but she might have easily been precipitated into such a condition had her white cells not risen to numbers of safety and normality. It is of interest that it was found that this patient had been taking "Novalgin" for arthritis of the spine, and during the period of observation it was noted that the taking of more "Novalgin" speedily caused her condition to become perceptibly worse and her leucocyte count to fall.

In the subacute type also relapses are apt to occur, and there are numbers of cases recorded in which apparent recovery was interrupted by a relapse which sometimes proved fatal. The possible occurrence of relapse shows the need for frequent examinations of the blood. The subacute neutropenias merge into an almost chronic state. It has been observed that among persons showing a low neutrophile and total leucocyte count there is a substantial proportion of those who complain of undue fatigue and depression of general health. These are possible candidates for a more severe neutropenic state, and attention should be directed not only to any red cell deficiency, but to the white cells also.

Cyclic Type.

An interesting variety known as the cyclic type is also recognized. C. A. Doan[9] has recorded the case of a girl of eighteen who was observed to suffer from a relative and absolute neutropenia in the blood every twenty or twenty-one days. There were no immature cells in the blood, and pentnucleotide treatment produced no effect. Fortunately the physical symptoms caused were few and slight.

Of greater interest is the case described by Rutledge, Hansen-Prüss and Thayer in 1929.[6] This most remarkable patient was then nineteen, and had suffered from attacks since childhood.

When he was a baby an excellent account of his first serious illness was written by M. Neale,[10] whose clinical acumen enabled him to recognize the striking features of the child's condition. These were recurring attacks of boils, with fever every few weeks, sometimes associated with necrotic lesions of the buccal mucous membrane and a leucopenia of 3,000 total white cells, the neutrophile cells being reduced to 1%.

Neale remarks that the "accompanying fever and prostration" were "all out of proportion to the clinical findings". This was written in 1910 long before the syndrome was described. This patient is unique, for he has been studied by various doctors all his life, and further interesting facts concerning him will be referred to later. Here it may be stated that he has continued to suffer relapsing

attacks, in which he becomes listless, sallow and tired, and while he has a rise in temperature ulcers appear on the gums; and associated with this disturbance is a regularly recurring leucopenia, the granular cells sometimes almost disappearing from the blood.

Pathology.

A brief summary of the pathology is here included, since the information is widely scattered through the literature.

The blood state may be again briefly referred to in order to stress the specific nature of the changes. No conspicuous degree of anæmia occurs, though as many of the patients are not young and not a few have been the subjects of more or less recent illness or debility, a red cell count in the region of four million or somewhat less per cubic millimetre is not uncommon and has no special bearing on the condition. The white cell count is rarely over 2,500 per cubic millimetre at the height of the illness, and it is probably fair to say that an illness throughout which the total leucocyte count is much over this figure is not likely to show the curious differential features of agranulocytosis, and is therefore not likely to fall in that category. The white cells in a number of recorded cases were 1,000 or less. In 103 cases analysed by Jackson and Parker,[11] in only seven was the count over 2,000; in 38 it fell between 1,000 and 2,000, in 28 between 500 and 1,000, and in 30 it was under 500 at the height of the illness. Only 7% of the total cases examined showed a proportion of 25% granulocytes among the total white cells. An interesting feature of the blood is the disappearance of the eosinophile cells, which have failed to reappear after clinical recovery for a period extending even to months. The eosinophile response observed in the course of successful treatment of pernicious anæmia may be referred to here in passing by way of contrast. The occasional increase in monocytes referred to above may reach a considerable figure, even up to 70% of the total. Platelet decrease has been described in association with the occasional hæmorrhages that are seen, but this is no essential part of the syndrome. It occurs most frequently in those blood disturbances following certain drugs, such as the organic arsenicals and gold.

There has been a great deal of confusion in describing the changes in the bone marrow. It must be remembered that the blood-forming marrow is a huge organ, scattered widely over various more or less inaccessible locations in the body. The average autopsy only samples it at random, for unless representative parts are examined it is obviously impossible to say just where the most intense or characteristic changes will be found. During life the difficulty is still more pronounced. Nevertheless, biopsy of the bone marrow has yielded interesting results. Sternal puncture is a practical procedure, as described by Reich and others.[12] Reich's technique is designed to remove enough material through a special trochar (introduced under local anæsthesia) to be mixed with a citrate solution and spun in a centrifuge. In this way a count of 1,000 cells may be made, and this may be taken as representative of at least part of the sternal marrow. This procedure may give evidence of maturation arrest on the one hand, or marrow aplasia on the other, and may help in prognosis and in the understanding of the condition. As regards the pathological changes found in the marrow after death, a consideration of the variations in the types of clinical illness observed will explain to some extent the variation in the findings recorded by different writers. The patient may die after a brief illness lasting days only, or may linger for several weeks, during which gradual exhaustion of the marrow may occur, with or without attempts at regeneration; or again, he may die from some intercurrent complication after regeneration has begun. These diverse states will cause diverse marrow pictures, for maturation of the granulocytes may be arrested, completely abolished, or more or less restored to normal. Moreover, examination of the marrow cells, like the blood cells, is probably only ideally accomplished by some vital method. At autopsy this is virtually impossible, and delay in fixation or the adoption of harsh fixation methods may result in misleading appearances. Allowance must be made also for the site from which samples are taken, for the marrow in the femur and tibia of the adult is normally fatty, while that of the vertebræ, ribs and sternum is normally cellular. The naked-eye appearance may be fallacious; Custer,[13] in his recent concise survey of this subject, points out that only microscopic examination can determine the number and nature of the cells of the marrow, from which sections should be cut after hardening, for no reliance can be placed on smears.

In fulminating cases hypoplasia of the marrow is usually found, with some degenerative changes. In the less acute some of the degenerative changes described by certain pathologists have been queried by others; Jackson and Parker[11] consider that they are seldom seen if a careful technique is followed. But the most characteristic change is the virtual absence of the more mature granular cells. In the normal active marrow there are few myeloblasts seen; reserve stocks are held as myelocytes and premyelocytes, these being adequate for all ordinary demands. But the agranulocytic marrow has been drained of all the young granular cells, and is distinguished by the large number of primitive non-granular stem cells. This explains in the main the hyperplastic condition which has been described and which has caused some confusion, and explains why a full marrow may be found and not an empty one as might be expected. The primitive cells multiply, but they cannot fulfil their destiny, and remain inactive and, in the absence of their maturation factor, powerless to supply the urgent need of the blood. Focal accumulations of lymphocytes and plasma cells are also found, but there is no replacement anæmia as in leuchæmia. The futile masses of primitive granular cells may show degeneration;

Jaffé[14] believed this was an essential disintegration of the granules of the young myelocytes, but Custer's view seems probably correct: that there is a sort of cellular progeria—the effete myelocytes die before they grow up. This author believes that he can distinguish the marrow of the essential agranulocytosis from that of a chemical or septic neutropenia since in the latter maturation arrest is not complete.

It is most important in describing the marrow changes to make clear just what is meant by "hypoplasia". Because the adult granular cells are missing, the condition is called hypoplastic by some writers, whereas there may actually be a normal or even increased number of primitive, that is, practically non-granular, cells present. Thus it is possible to find practically identical illustrations in the literature labelled "hypoplasia of the marrow" by one writer and "hyperplasia" by another—a confusion due chiefly to inadequacy of definition.

The pathology of the other organs may be briefly dismissed. The systemic organs, such as heart, liver *et cetera*, may show cellular spoiling, as is seen in acute toxic states; bronchopneumonia sometimes occurs, and the appearance of the lung may suggest infarction rather than a true pneumonitis. The lymph nodes may be enlarged and show hæmorrhages, and the germinal centres are more or less inactive. Suppuration is rare, as might be expected, since pus-forming cells are so scanty. A very instructive case, for which I am indebted to Dr. O. A. A. Diethelm, illustrates this.

CASE IV.—A middle-aged woman suffered from a septic laceration of the head. She entered hospital extremely ill, with a temperature of 40·5° C. (105° F.). Her blood count revealed a total white cell tally of 1,600 per cubic millimetre, with 18% neutrophile cells, 80% lymphocytes and 2% monocytes; the red cells numbered 4,700,000. After twelve days of severe illness a large swelling formed on the neck, and though no pus was obtained on incision, a *Staphylococcus aureus* was grown on culture. Four days later a further glandular swelling formed, but incision failed to evacuate pus.

This is in keeping with what is known of leucopenic states, for pus cannot be formed in the virtual absence of the cells that are characteristic of it. Eventually this patient made a good recovery. Her case appears to illustrate the possible rôle of septic infection in depressing the bone marrow activity, though it must be pointed out that we are not by any means sure that there were not preexisting factors which interfered with and temporarily paralysed granulopoiesis, the infection being a secondary event.

One last point of interest in the pathology is to consider what happens when the granular cells disappear from the blood. Plum,[2] in a recent excellent account of seven cases, comments on the surprising rapidity with which the granulocytes may leave the blood stream. In the case of one patient he made observations every five minutes during the performance of a blood transfusion and found that the leucocytes actually decreased in number during the transfusion; in fact in only one specimen of blood were granular cells found. He could demonstrate no destruction of these cells of the donor's blood when they were immersed in the serum of the patient *in vitro*, and considers it unlikely that the cells are rapidly disintegrated. He suggests instead that the granulocytes may wander along the capillary walls; and shows mathematically that undue adhesiveness of these cells to the capillary walls would soon remove them entirely from the circulation. But it is by no means certain that rapid destruction of the granulocytes does not occur; exaggeration of the normal "waves of death" among them might soon account for their disappearance. Attention should here be drawn to the work of Doan[15] and associates, who, in investigating the effect of nucleic acid split products on leucocyte response in animals, found that an initial drop in the number of circulating granulocytes occurred. This was found to be due to collection of these cells in the spleen, and could be prevented by splenectomy. The rôle of the spleen in granulopenia seems obscure, but its possibilities should be remembered. Further investigations of the blood chemistry in cases of agranulocytosis could be carried out with advantage, especially to study any fluctuations that might occur in the uric acid content of the blood.

Finally, there are very definite grounds for stating that the initial change in agranulocytosis occurs in the bone marrow; this stage is followed after an interval by the typical changes in the white blood cells of the circulating blood, and still later the clinical onset of the disease occurs.

Ætiology.

Ætiology is the most interesting chapter in this clinical and pathological story. Wrapped up with it is the question of the nature of the condition. Is it a separate "disease", or rather a syndrome occurring as the result of various causes? The latter seems to be nearer the truth, as will be seen; and, if this view be adopted, the artificial classification of the so-called primary and secondary types of some authors is avoided.

First, there is the question of infection. For some years there was a controversy centred on the problem of which came first, the granulopenia or the infection. Several organisms were specifically blamed for the whole condition, chief of these being the Vincent fuso-spirochæte. It is now known that the infections are secondary, for, although experimental neutropenia has been induced in animals by massive infections, the results of such experiments are not comparable with the condition as seen in man. Further, study of the recurrent forms of the disease and of relapses in single attacks has proved that the blood changes antedate the infections—the fall in granulocytes is well established before the mucosal lesions appear. Many writers speak of poor leucocyte response in acute infections, but surely this is uncommon. I have recently looked through numbers of leucocyte counts in acute infections in the hæmatological records of the Royal

Prince Alfred Hospital, and it is striking to observe the remarkable constancy with which the white cells respond. Even though the total counts may not always be high, the neutrophile percentage rises almost invariably—this of course does not refer to those types of infection that are known to cause a slight fall in the relative number of granular cells, such as typhoid fever. Here a remark may be interpolated concerning the leucopenia that is so common a feature in pernicious anæmia. Perhaps further research will reveal what it is that causes this; it would be of interest to know if it depends on the same defect that lowers the red cell numbers. But as regards the so-called poor leucocytic response sometimes seen in acute infections, it would seem that this is a danger that may threaten the person whose neutrophile cells are always on rather a low level. Then it is that some event, such as infection or the absorption of a toxic drug or other unknown factor, may reduce the granulocytes to a degree which may be incompatible with life. There are, of course, cases of extremely intense infection in which the marrow function is dangerously depressed. It must be remembered that a vicious circle may be set up, for if the neutrophile cells sink below, say, 2,000 per cubic millimetre, the capacity to resist infection will be very small indeed; the case of chronic neutropenia quoted above illustrates this.

An example of the celerity with which a fatal general infection may ensue when the granulocytes disappear from the blood may be found in the following case, quoted by courtesy of Dr. C. G. McDonald.

CASE V.—A woman, aged forty-three years, had previously been healthy, except for an attack of sore throat three years ago, lasting a fortnight. She was strong and robust in type, and when first seen complained of a sore throat, which had been self-treated for six days. There was a little furry exudate on the fauces, but her general condition was quite good. The next day there was a dramatic change in her appearance; she looked ill and weak, the respirations were rapid, but no signs were found in the chest. Agranulocytosis was suspected because of the rapid change for the worse, and a blood count by Dr. Tebbutt revealed only 750 white cells to the cubic millimetre; only one degenerate neutrophile cell was seen. A curious vesicated lesion on the skin of the arm was found to contain *Staphylococcus aureus*, and blood culture yielded growths of the same organism. A blood transfusion of 750 cubic centimetres was given without avail, and the patient died on the fourth day after coming under observation.

There can be little doubt here that the fatal blood infection was a secondary event.

One interesting possibility in connexion with sepsis and granulopenia is that focal sepsis may play some part at least as a predisposing cause. Dennis[30] has demonstrated that granulopenia may be produced in rabbits by introducing sealed parchment capsules containing streptococci into their peritoneal cavities. He claims that a toxin, leucocidin, is generated which is lethal to the granular leucocytes and inhibits their formation. These experiments are suggestive, especially when taken with findings such as those of Daland.[32] This author has described a small lymphocyte increase in the blood of those proved to have active dental periapical sepsis, with corresponding decrease in the neutrophile cells. No such condition was observed in other chronic disease unassociated with apical infection, and the lymphocytosis and granulopenia disappeared when the sepsis had been eradicated.

The causes of agranulocytosis may be perhaps divided into predisposing and determining. Among the former are perhaps sex, the menstrual cycle, endocrine disturbances, previous illness, debility, excessive fatigue, natural hypersensitiveness to some of the known chemical determining causes, and perhaps the deficiency of some factor or factors that aid in maturing the granulocytes. The question of sex incidence is most interesting. While cases occur at any age and in either sex, the majority have been observed in women, and a large percentage of these have been at or after middle life. Further, a definite association with the menstrual period has been observed—Case II may here be cited. Jackson and Merrill[16] describe the case of a patient who had a definite granulopenia at the beginning of each menstrual period. This is not usual; Rowe and Guaginty[17] found that the influence of the catamenia on the leucocytes was very slight in a normal series. These facts suggest the possibility of an endocrine factor, and reference must be made here to the fascinating case, already referred to, of the man who has suffered lifelong cyclic attacks of neutropenia. W. P. Thompson[18] has been able to follow the later career of this man and has studied his urinary excretion of female sex hormone. Quite large amounts of sex hormones were excreted by this patient, and considerable fluctuations occurred corresponding to the attacks of neutropenia. He also suffers from *diabetes insipidus*, which is amenable to pituitrin. It is impossible to avoid the conclusion that some rhythmic pituitary anomaly is concerned in these cyclic attacks. The influence of endocrine disturbances as a predisposing factor in other cases is also conceivable. The existence of previous disease in many of the recorded cases introduces a disturbing factor, for there is no means of knowing what kind and degree of alteration in body function is thus produced. The effect of illness and fatigue on digestion may be cited, also that of mental stress, the importance of which must be recognized in a great variety of diseased states by all practising physicians. One very interesting possibility has been raised in connexion with bodily fatigue. It has been mentioned previously that among the persons whose leucocyte counts are on the low side of normal or below normal are many who suffer readily from bodily fatigue, though they present no evident sign of disease. It is conceivable that such persons might be more likely subjects of the agranulocytic syndrome than others, but, of course, this is pure assumption. The possibility of a deficiency in the hypothetical maturation factor for granular leucocytes has been mentioned; there is no proof of anything of this kind, but it is not unreasonable to regard it as at least not improbable. The question of a dietetic factor has also been

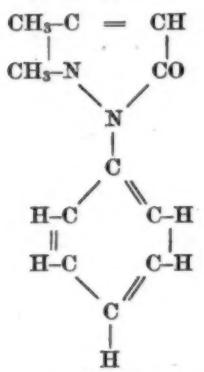
raised in connexion with the experimental neutropenias in dogs, and in this connexion it is interesting to recall the work of Doan,[19] who was able to reduce the bone marrow in pigeons by underfeeding, and to remember also the aid given in blood regeneration by a diet rich in the vitamin *B* complex.

Lastly, we must consider the very important question of the effect of undue sensitiveness to certain drugs.

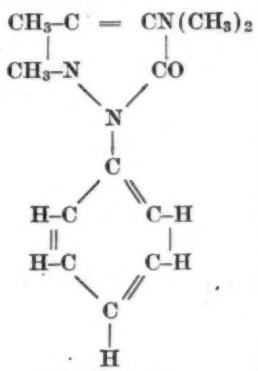
Allergy is a popular explanation of many pathological processes today, but even being careful not merely to follow a fashion, it must be admitted that this is of real importance here. Agranulocytosis is known to be an occasional sequel of medication by many drugs, including the organic arsenicals, gold, dinitrophenol and other benzene derivatives, and, more particularly, amidopyrine. A few cases have been reported in which granulopenia ensued after the administration of the first named groups, but these are only rare events, comparable with the occasional occurrence of purpura in similar circumstances. So much has been written lately about the possible toxic effect of amidopyrine that it is worthy of closer study. Amidopyrine was prepared by Stolz forty-two years ago, and four years after that it was patented in Germany under the trade name of "Pyramidon". It has been sold in America as amidopyrine for thirteen years, and in the last ten years has been a drug of increasing popularity, especially since the introduction of synthetic drugs combining it with various of the barbiturates. Several observers in America, particularly Madison and Squier,[20] have pointed out that, first, the period over which agranulocytosis has been widely recognized coincides with that over which amidopyrine has been used in medicine, and, secondly, that in a considerable proportion of investigated cases there was a clear history of taking this drug. In several countries, notably America and on the continent of Europe, the proportion of cases in which such a history was obtained has been found to be strikingly high. Negative information is afforded by the figures recorded by Custer,[13] who states, that during 1934, 29,488 patients were admitted to the Philadelphia General Hospital, with 4,027 deaths and 1,926 autopsies. He remarks that no *post mortem* evidence of a single case of agranulocytosis was available, nor was there any record of patients who recovered; against this is to be set the fact that 120,000 tablets of amidopyrine were used in the hospital during the year. Many cases have been reported recently, and Plum has collected 128 cases in about eighteen months in which agranulocytosis occurred after the taking of therapeutic doses of amidopyrine. Of these, 70 were fatal. That it is not merely a matter of coincidence is now proved beyond a doubt, for several patients who have recovered have suffered a recurrence on taking the drug again. Even one dose of 0·3 gramme (five grains) or less has precipitated a typical attack in a sensitive patient. It must surely be assumed that here we are faced with a condition of hypersensitiveness to the drug, whatever may be the predisposing factors. In such cases it would appear that the syndrome may be a special expression of anaphylaxis. But it must not be thought that amidopyrine is to be incriminated in all cases, as some have suggested. In some instances there has been no history of any medication by drugs, and in a few cases the patient has recovered although amidopyrine was administered throughout the illness. The matter is well summed up in a special report of the Council on Pharmacy and Chemistry of the American Medical Association,[21] in which it is stated that no other agent, either chemical or bacterial, has been a factor in so many cases as amidopyrine. In most reported cases the drug has been taken in combination with one or other of the barbiturate drugs, and it is assumed by some that there may be some synergic action exerted by the latter group. That the barbiturates alone are innocent in this regard there is no doubt, for they have had an extraordinary popularity without any such toxic action being observed, and the toxicology of the barbiturate group is so well known that no uncertainty can exist in this respect. It is not even necessary to postulate a synergic action between the two drugs, for amidopyrine is probably more used in combination with the barbiturates than in any other form, on account of the particular advantage in combining an analgesic with a sedative. Animal experiments have proved that granulopenia can be caused by the administration of amidopyrine, but these are always much less convincing than observations on the human subject. Indeed, experiments on laboratory animals are apt to be misleading when the toxicity of drugs is being investigated, owing to the variation of action in different species. Some of the cases recorded in the literature in which a patient who had recovered from agranulocytosis had a definite attack provoked by a single small dose, are most instructive. The sequence of shivering, malaise, rise in temperature, and a signal fall in the total leucocytes, particularly the granular cells, is most convincing. In other words, the syndrome has been reproduced by a minimal dose of the chemical cause, sensitization having once been established. It is of particular interest to observe that in Plum's case the white cells had fallen from 9,000 to 1,900 in one and a half hours, and during the height of the reaction the urine gave a reaction to the test for urobilin. This rise in leucocytes was followed by a transient secondary rise, and this by a more prolonged fall, affecting especially the granulocytes.

It is a fascinating inquiry to examine the chemical nature of the offending drug in the endeavour to find why it exerts this peculiar action in some cases. Writers on the topic speak glibly of the toxic action of the benzene ring derivatives, and give such examples as the organic arsenicals, which contain combined rings. But this suggests that the benzene ring is of necessity toxic, a statement that is only partly true. Benzene itself is certainly a depressant of hæmopoiesis, and is used for this purpose. Phenol and the aniline type drugs,

such as acetanilide and phenacetin, can cause blood destruction in appropriate doses; phenylhydrazine is a potent reducer of the circulating red cells, but other drugs, such as the salicylates, are relatively innocuous. It would appear that the benzene ring is not of itself necessarily harmful, nor are all the "benzamine" group of drugs toxic to leucocytes. Amidopyrine, loosely spoken of as a benzene ring derivative, is really much more than this. It contains the benzene ring in combination with the pyrazalon complex, which is derived from pyrrhol. Is it the latter group that is toxic? Some writers, like Herz,[22] seem to think so, yet phenazone or antipyrine is a precursor substance to amidopyrine and contains the same groups, although there is no evidence that it can be regarded as being as toxic to leucocytes as the latter drug. Diethelm's case, quoted above, shows that certain other drugs containing the pyrazolon group may be toxic to white blood cell formation, for "Novalgin", the drug in question here, is an amidopyrine derivative, being described as sodium phenyl-dimethyl-pyrazolon-methyl-amino-methane-sulphonate. Reference to the structural formulæ will show that the only difference between the two drugs, antipyrine and amidopyrine, is the possession by amidopyrine of an amido group (NH_2), in which H is replaced by a methyl group (CH_3). The NH and NH_2 groups appear to confer



Antipyrine.



Amidopyrine (Di-methyl-amino Antipyrine).

toxic properties on some compounds, and this may be the explanation in part, but it must be pointed out that a very small alteration in a structural formula may make a huge difference in the result when the substance is absorbed into the animal body. This possible difference in the effects of closely related drugs is a very important one for the clinician to bear in mind; the practical variations in the clinical effects of different members of the barbiturate family may be cited as a familiar example.

It seems remarkable that there is so little evidence of amidopyrine granulopenia in Australia. Most of the cases observed locally cannot be set down as due to this cause, though some doubts exist, as in Case II quoted above. It may be that more strict inquiry is necessary, as has been found in cases recorded elsewhere, for there seems no doubt that amidopyrine is used here to a considerable extent. Perhaps as time goes on more instances of sensitization to this drug will be observed. A case may here be quoted in which it is possible that drug therapy of some kind may have been an exciting factor. Dr. Lorimer Dods has kindly provided me with notes of this patient, whose illness ran the following course.

CASE VI.—A male, aged twenty-nine years, had suffered from spondylitis for four years, but was otherwise well. The only drugs given had been aspirin, phenacetin, other salicylates and iodides until two weeks before the illness, when he had been given the last of a series of injections of some unknown preparation, thought to be sulphur compound. When first seen he had a stomatitis and gingivitis that suggested a Vincent's infection, and within twenty-four hours, though the local lesions had not spread, his condition had become much worse. A blood count revealed a very definite leucopenia and granulopenia, and within three days the total white cell count was reduced to 600, and no granular cells could be seen. The next day the total leucocyte count was only 400, with no granulocytes, and some signs of pneumonia were discovered. The patient's condition seemed desperate, but from this day there was a steady rise in the total white cell count, with a coincident return of the granular leucocytes. For the next week his state was one of great anxiety and consolidation of both lungs was observed. Treatment included three whole blood transfusions, one stimulating dose of X rays, and local and intravenous use of "Novarsenobillon"; no "Pentnucleotide" was then available. He recovered after a long convalescence, and periodic examination of the blood for the last two years has not revealed any abnormality.

Dr. Dods observed that the improvement in the blood state seemed to date from the clinical onset of the pneumonia, and thinks that this was the turning point in the illness rather than the specific effect of any treatment.

The possible causes of agranulocytosis may be roughly summarized in the following list, which is intended to be suggestive without making pretensions to accuracy.

Predisposing Causes:

Sex, age, previous illness, debility and fatigue.
Preexisting leucopenia.
Menstrual cycle.
Lack of granulocyte maturation factor, due to ? metabolic defect, ? dietary defect, or ? endocrine defect.
Natural or acquired hypersensitiveness to some known or unknown exogenous factor, for example, drug such as amidopyrine.
? Focal sepsis.

Precipitating factors:

Drugs, for example, amidopyrine, gold, arsphenamine, dinitrobenzol *et cetera*.
Infection, probably only where granulopenia already exists, except in certain cases of intense systemic infection.
Endogenous factor, such as ? perverted metabolite.

Diagnosis.

The rarity of the syndrome is undoubted, but as is the case with all rare diseases, it is probably not always recognized. The possibility should always be borne in mind in all suspicious cases, and a full blood count made, as prompt diagnosis is so important. Certain other states are sometimes confused, though they should not, if adequate blood examination is made.

Acute or Overwhelming Sepsis or Other Infection.—An unusual depression of granulocyte formation may occur, for instance in a disease such as typhoid fever, which is constantly associated with granulopenia. This may assume the true character of the agranulocytic syndrome, as in the case reported by Blackie,[23] but as a rule the degree of white cell reduction is only moderate, and, as already pointed out, leucocytosis, or at least a relative increase in the granular cells, is extremely constant in infective states.

Acute Pharyngitis of Other Types.—Diphtheria perhaps only needs mention. It is important, however, to make sure that what is apparently a primary Vincent's infection of the pharynx is not confused with the agranulocytic angina, since the prognosis is so different.

Great Lowering of the White Cell Count with Severe Anæmia.—Conspicuous lowering of the white cell count is often seen in pernicious anæmia, for example, but this is entirely different, and is in no way part of the agranulocytic syndrome. Aplastic anæmia is likewise quite distinct.

Acute Leuchæmia.—Without doubt an acute myeloblastic form of leuchæmia is often confused with severe essential granulopenia, owing to the false idea that a raised white cell count is *per se* a necessary part of the blood picture in leuchæmia. It is the qualitative change which is distinctive, and if this were generally admitted there would be no need for that ridiculous and unnecessary term "aleuchæmic leuchæmia". The appearance of precursor cells in the blood stream, together with a definite and usually severe anæmia, makes a sharp distinction between this state and that under discussion. Immature granulocytes, that is, myelocytes and myeloblasts, are not seen in the blood in agranulocytosis, except to some extent in the recovery period, when an early sign of improvement may be a transitory appearance of myelocytes. If considerable anæmia is present, it is unlikely that the illness is a true essential granulopenia, and if there is a high proportion of granular cells, however immature, the matter is beyond doubt. It may be also remarked that the leuchæmic patient for a considerable time often shows a much less degree of depression of health than might be expected; the striking prostration typical of the severe neutropenias is not seen until late in the illness. The difficulty that may exist in diagnosis is shown by the case commented on by Jackson and Parker,[11] whose patient apparently had a true agranulocytosis and subsequently died of leuchæmia. I cannot help feeling that this was a case of leuchæmia from the beginning.

Infectious Mononucleosis (Glandular Fever).—Infectious mononucleosis may cause some difficulty on account of the high percentage of mononuclear cells that are occasionally found in the blood in certain phases of agranulocytosis. The glandular swellings do not rule out the latter, however, though they are seldom very large. A study of the patient's general state should soon make the picture clear, and if attention is paid to the level of neutrophile cells in the blood rather than to the excess of monocytes, confusion should not arise.

Treatment.

Treatment has not been strikingly successful on the whole, but an advance has been made in the introduction of pentose neucleotide. The history of this remedy goes back to the days of frequent sepsis and "laudable" pus. Pus was readily obtained as an object of investigation in those early days, and from it nucleic acid was prepared, being so called because it was believed to be chiefly derived from the nuclei of leucocytes and other cells. Later it was found that nucleic acids occur in combination with various proteins in the form of nucleoproteins, for instance, in lymph glands, thymus, spleen, liver and hæmopoietic tissues. By process of hydrolysis the purine bases adenine and guanine were isolated, and derived from these was the pentose nucleotide, found to exist chiefly in the nuclei of living cells. Jackson then isolated it from the blood, which was an observation of importance, since it had been found that all these products and split products of broken-down cells such as leucocytes had some effect in enhancing granulopoiesis. As has been pointed out above, there is some reason to believe that these split products may be a natural stimulus to further leucocyte production and maturation.

A preparation known as "Nucleotide K 96" was used therapeutically in agranulocytosis, and as it seemed to be of promise its production was standardized and the drug marketed as "Pentnucleotide". There is no positive proof that this supplies the hypothetical maturation factor. It has been suggested that it contains a chemotactic principle only, and that where maturation is abrogated "Pentnucleotide" cannot be of service, and that its usefulness is confined to cases in which there is only maturation arrest. There is, however, a latent period of some days observed in some cases in which success has appeared to follow its use, suggesting rather that the more primitive cells are stimulated to mature by the drug. Beck[24] suggested that where myeloid hyperplasia or even hypoplasia of slight grade was present in the marrow, the case was a suitable one for "Pentnucleotide", since here only the chemotactic factor was lacking. This is probably not true, however, as the hyperplasia is due to the collection of myeloblasts that are arrested in development, and a maturation factor would thus be necessary to overcome this arrest. Perhaps sternal puncture might aid in exact diagnosis of the degree of cellular arrest that is present in the marrow, but this seems a refinement, and surely it is wise to employ in every case a remedy that does seem to be of service in this fatal disease. "Pentnucleotide" is a water-soluble and non-irritating product, and is given in doses of 0·7 gramme, dissolved in 10·0 cubic centimetres of water. This dose is given twice daily by intramuscular injection until the count becomes normal, or at least until a substantial improvement is observed. This dose may

be doubled in severe cases. The drug is suitable for intravenous injection, but reactions of varying degree have been observed following its direct introduction into the blood, and probably the intramuscular route is sufficiently direct even in acute cases. If blood transfusion is being used, the "Pentnucleotide" may be added to the volume of blood introduced.

The exact value of "Pentnucleotide" in treatment cannot yet be stated. Agranulocytosis is a curious disease in which the arrest in granulocyte production may spontaneously terminate at any moment, as study of reported cases will show. Nevertheless the figures showing results of treatment with this agent are very encouraging, up to 75% of recoveries being claimed in some series. Thus Jackson, Parker and Taylor[1][25] record some good series, including 69 patients, of whom 51 recovered. "Pentnucleotide" is useless in myeloid leuchæmia, so that accurate diagnosis is necessary in collecting cases. There seems no doubt, however, that in severe granulopenia it is more useful than any other drug hitherto employed. If improvement occurs after the administration of "Pentnucleotide" it may occur quickly, but the typical response takes place only after three to five days, time having been given for the young cells to mature and enter the blood stream. It has been pointed out that this latent period curiously resembles that seen in pernicious anæmia before the typical reticulocyte response is seen following liver therapy. A leucocyte cream has been employed by Strumia,[26] but this involves technical difficulties which make it an unduly cumbersome method. Transfusion of blood is a logical means of treatment, and though its value is uncertain, it should be used in all severe cases, repeatedly if necessary, since it must be realized that it is probable that in some cases of agranulocytosis the arrested granulopoietic function will recover if the danger period can but be tided over. Consideration of the function of the granular leucocyte as a source of complement suggests the use of fresh serum from a donor, and the occasional success obtained by this means in certain infections should encourage us to try it here, though I have not seen any reports of its use in the literature.

Liver extract has been widely used also. Its value is doubtful; as pointed out above, liver therapy in pernicious anæmia causes an increase in the leucocytes, but whether this stimulating effect is to be looked for in granulopenia is uncertain. However, it cannot do any harm to give a good extract by intramuscular injection. Apart from this, any existing anæmia, of course, needs appropriate treatment.

Injections of irritants like turpentine (0·3 to 0·6 cubic centimetre or five to ten minims) under the skin, in the hope of forming an artificial abscess by attracting pus cells, have been tried, but in spite of a favourable report by Roberts and Kracke[27] it is not recommended by the majority of writers.

So-called stimulating doses of X rays to the long bones have been used by numbers of workers. One-twentieth of the erythema dose as recommended by Taussig and Schnoebelen[28] may be used, with the object of stimulating the marrow, and apparently some measure of success has attended this procedure. It has been suggested by Beck that any result attained has not been due to any direct stimulation, but rather to the breaking down of some of the myeloid foci where immature granulocytes are collected, with the setting free of split products of these cells, thereby supplying the missing maturation factor. X ray therapy seems to me to be a dangerous weapon, for how are we to estimate the nature and amount of the marrow reaction in such a serious morbid state? Can we be sure that the granulopoietic function is being stimulated, or are we quenching the smoking flax?

The mucosal lesions should be treated *secundum artem*, but no surgical intervention is desirable. The use of arsenicals for the Vincent's infection might perhaps be queried, owing to the occasional toxic action of these drugs on the bone marrow. Probably the risk is very small, but perhaps it is sufficient only to employ the arsenic locally. If analgesics are used, it is certainly inadvisable to prescribe amidopyrine.

One vital point in treatment is that it must be controlled by frequent blood counts, for the blood state is the only accurate guide. Should the patient relapse, the first warning will be given by the blood and not by his clinical state; active treatment should be resumed immediately in this case.

The Nature of Agranulocytosis in Regard to Prophylaxis.

It is of interest and importance to consider what is the nature of this curious condition. It is probably correct to regard it as a pathological syndrome rather than a disease. It is a picture which may be due to a combination of causes, and every effort should be made to take an accurate history of any case and to make observations as complete as possible in order that some light may be shed on its dark places. Lescher and Hubble,[29] in a thoughtful review of the subject of hypoplasia of the bone marrow, point out that any one of the three varieties of cells arising from this organ may go out of production. It is not that the cellular elements of the blood become obsolete too rapidly, but that some of the essential material or machinery is lacking in the factory. Thus a defect in the essential factors that control production may produce, in the case of red cells, an essential anæmia, such as pernicious anæmia; in the case of the platelets, thrombocytopenic purpura; and in the case of the granular leucocytes, an essential granulopenia. A break-down in all three would cause an aplastic anæmia. It is interesting to recall, as these writers point out, that benzol may produce any one of these in a more or less pure form.

As regards prophylaxis there is not much to be said. Correct diet, containing all the substances known to be of hæmopoietic importance, might do

something towards reducing the risk of a relative neutropenia, just as it will that of an anæmia. This is important in elderly people. Where drugs are used that are known to have the power of reducing the white cell count, care should be employed and toxic reactions looked for. Should amidopyrine be used at all? Certainly practically all the recorded cases following its use have ensued on continued administration, even though moderate doses were used. Unlimited medication with amidopyrine is fraught with a certain degree of danger, particularly in persons in middle life, and especially women. Probably there is not much risk in the use of an occasional dose, especially in young people, for example, a dose or two each month for dysmenorrhœa (for which it is largely prescribed). Yet it is well to remember that an occasional person might become sensitized thereby, and should suspicious, even though transient, symptoms be noticed after a dose, it would be wise to have the white blood cells counted. In view of the apparently small degree of susceptibility of the community as a whole to this drug, it might be suggested that the risk is not greater than that of toxic liver necrosis following the use of the cinchophen drugs. But even this suggestion is made with diffidence. It has been proposed that the use of the drug should be controlled by blood counts, but surely this is a needlessly cumbersome and unpractical idea, for, after all, there is no need to use it at all, as it is readily replaced by other analgesics. Sensitivity cannot be ascertained by skin tests, for agranulocytosis has been observed without any evidence of skin allergy, so there is no means of finding out who is sensitive to the drug.

It would seem to be inadvisable for such drugs as amidopyrine to be available to the public except by medical prescription. Its frequent combination with a barbiturate is a certain safeguard, since the latter group of drugs are not freely saleable by law; but this is only so in the case of those preparations that actually come within the scope of the legal definition. Certainly it is imperative for the practitioner to know exactly what is in the proprietary preparations that are so seductively brought under his notice by the various drug firms. The chemical constitution is stated on the packages and in the accompanying literature, but this will convey very little to the average doctor, who is not an organic chemist, and the information is not infrequently conveyed in small type that does not encourage inquiry by the presbyopic. For example, it may not be very enlightening to read that a drug is not a poison and that its composition is brom-iso-valerianyl urea with dimethyl-amidophenyl-dimethyl-iso-pyrazolon. Without attempting to compile a complete list of all the relevant proprietary drugs, it may be of interest to point out that the following preparations (all of which may not be familiar to Australian prescribers) contain amidopyrine, in many cases combined with some sedative, such as a barbiturate: "Compral", "Veramon", "Amytal compound", "Gardan", "Asciatine", "Etipiron", "Diallylpyrine", "Cibalgin", "Geamine", "Trigemin", "Dysmenol", "Amidophen", "Sedalyl", "Allonal", "Klimaxid", "Prokliman", "Somnosal", "Hebaral sodium" with amidopyrine, "Neurodyne", "Optalidon" and "Yeast-vite". "Pyramidon" is the original trade name for amidopyrine, and "Novalgin" is a closely related derivative. Since compiling the above I find the Report of the Ministry of Health contains a similar list. This list omits a number of the above, but includes in addition the following: "Anestan", "Benzedo compound", "Dodo", "Eupaco", "Hexin", "Midol", "Sedal" and "Yeast tonic tablets". It will be seen that the compilation of such a list is not easy; but what is easy is for both the prescriber and the public to use drugs the true composition of which is not always apparent.

Conclusion.

In conclusion I stress the need for further investigation into this remarkable disease complex. What is it that arrests the development of those all-important cells, the granular leucocytes? And why is it that even the multiplying stem cells of the marrow fail to pass over into the blood stream? It is our duty to be on the watch for cases of granulopenia, not only that we may institute early treatment for a morbid state which may threaten life, but that we may study more closely processes whose mechanism, even under conditions of health, is not clearly understood.

Summary.

The need for a strict definition of the fully developed syndrome of agranulocytosis has been stressed, as well as the value of accurate records of observed cases.

The importance of recognizing the chronic and recurring cases has been pointed out.

The invaluable help given by blood counts in all cases that suggest the possibility of a granulopenia is emphasized.

The symptoms, pathology, diagnosis and treatment have been briefly traversed.

The various factors in ætiology have been discussed, with special reference to the position as regards amidopyrine and the possibilities of prophylaxis.

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THE ESTABLISHMENT OF "MOSSMAN", "COASTAL" AND OTHER PREVIOUSLY UNCLASSIFIED FEVERS OF NORTH QUEENSLAND AS ENDEMIC TYPHUS.

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THE belief has existed for many years that some of the unclassified fevers of North Queensland were endemic typhus, and odd cases have been shown by serological tests to be of this nature. The great majority of cases of these fevers, however, have been called up to the present by names indicating locality or occupation, and their exact nature has not been recognized.

The recorded work done in the past by workers, including Smithson, Clarke, Breinl, Cilento, Baldwin, Wheatland and Heydon, has been directed more to an analysis and comparison of clinical types and to a survey of epidemiological aspects. No details of an approach to the differentiating of the fevers by systematic serological tests with the *Bacillus proteus* X 19 group have been recorded, though between the years 1927 and 1929 Paine and Nye diagnosed several cases of endemic typhus, the results being confirmed at the Australian Institute of Tropical Medicine, Townsville. These results were not published.

In the present preliminary contribution complete proof is given that the fevers now (June, 1935) occurring in Mossman, Cairns and Tully are endemic typhus. In the past one of the main difficulties in classifying the fevers has been the diversity of clinical types. In the series at present recorded there have occurred both mild and severe cases (one death), cases with varying degrees of enlargement of lymph glands and cases without enlargement of lymph glands, cases with rash and cases without rash, cases with fever of short duration and cases with fever of long duration. In all the diagnosis has been confirmed by a positive result to the Weil-Felix test.

In addition, evidence is adduced to prove beyond reasonable doubt that the great majority of cases of fever occurring in the coastal belt from Tully to Mossman in the past twenty years have been endemic typhus, and an explanation of the failure to establish the diagnosis previously by serological tests is provided.

Clinical Notes.[1]

CASE I.—H.D., male, aged forty-seven years, unemployed, was resident in Cairns. He was first taken ill on May 6, 1935. He had been fishing up the inlet three days previously and had been bitten by insects. He felt "dopey" and tired, and went to bed on May 8 with severe frontal headache and fever. He got out of bed on June 9 to look for employment and had two severe shivering attacks. He reported to hospital and was admitted on May 11, com-

[1] Two typical temperature charts are published herewith.

plaining of severe headache. He developed a rash not unlike rose spots on May 13, and the result of his Weil-Felix test was positive with the Warsaw strain on the same day. His face was flushed and his bowels were constipated and he continued to have headache and insomnia until May 16. The temperature resolved by lysis and became normal on May 20. He was discharged from hospital on May 30.

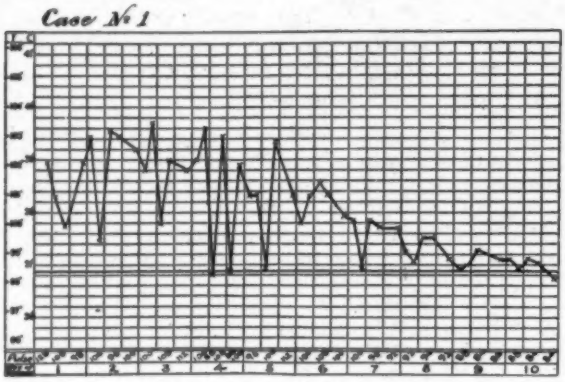

FIGURE I.
Chart in Case I, typical of a patient who recovered.

CASE II.—A.C., male, aged thirty-four years, farm worker, resident at Hambledon, was taken ill on May 15, 1935, with frontal headache and fever; he complained of feeling tired. He was admitted to hospital on May 25 with a temperature of 38·9° C. (102° F.), a severe headache, a flushed face and lassitude. He continued in this condition for five days, drowsiness being very pronounced. It was necessary to arouse him to interrogate him, and he replied slowly but sensibly to questions. After the fifth day his temperature remained normal and he was discharged on June 7. His blood gave a positive reaction to the Weil-Felix test, Kingsbury strain, on May 27.

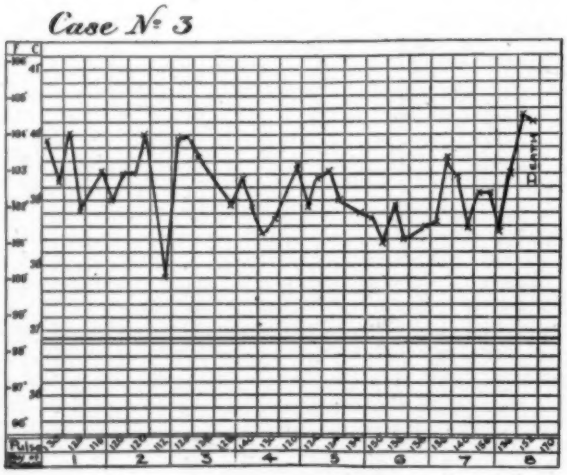

FIGURE II.
Chart in Case III, typical of a fatal infection.

CASE III.—M.S., female, aged fifty-five years, lived at Hambledon sugar mill; she was engaged in domestic duties. She was in the habit of going with her husband into the scrub to gather decayed leaves, bark *et cetera* for her fern baskets. She took ill on May 26, 1935, with a feeling of tiredness and headache. She had attacks of vomiting and was unable to retain food. She was seen by one of us (A.M.L.) on May 30. Her temperature was 39·4° C. (103° F.), the tongue was furred, she was complaining of frontal headache and vomiting. She was admitted to hospital on June 3. Her temperature was 39·7° C. (103·5° F.) and pulse rate 130 per minute. She was suffering with great prostration. On June 5 she developed a profuse macular rash on the face, body and limbs. The Weil-Felix test on June 4 gave no reaction. She continued acutely ill (typhoid state) and died on June 11. The Weil-Felix test gave a positive reaction on June 10 with the Kingsbury strain.

CASE IV.—L.M., male, aged nineteen years, unemployed, was living on the edge of the scrub near Hambledon. He first felt ill on June 2. He stated that he felt "dopey" on June 5. He commenced to get a frontal headache and had a shivering attack on the same day. Next day he felt feverish and appeared to have had a severe rigor. He was admitted to hospital on June 9, and on the following day developed severe pain in the back of the neck. The tongue was furred and insomnia was marked. The Weil-Felix test gave no reaction. About June 14 the temperature was not so high and his general condition had improved. On June 15 he complained of pain in the left side and developed lobar pneumonia. On June 17 the Weil-Felix test gave a positive reaction with the Kingsbury strain.

CASE V.—N.S., a female, aged fourteen years, a schoolgirl, was residing near Hambledon. Her illness began on May 28, 1935, with lassitude and fever. She was admitted to hospital and remained in hospital until June 14. There was a macular rash and enlargement of the axillary glands. The temperature ranged from 38·3° to 40° C. (101° to 104° F.) and resolved by lysis on the fifteenth day. The Weil-Felix test gave a positive reaction (Kingsbury) on June 14.

CASE VI.—H.M., male, aged thirty-one years, was living at Mossman and was employed in butchering work. His illness began on May 13, 1935, with headache and pains in the limbs; he was admitted to hospital on May 20. The temperature was 38·1° C. (100·6° F.) and his pulse rate was 88. He was very ill and complained of intense headache, particularly over the frontal region, and of intense pains in the limbs. The conjunctivæ were congested and the brows were wrinkled. The glands of the neck were enlarged. The spleen was not palpable. A rash was beginning to appear. The fever continued for twelve days after his admission to hospital. The rash remained for ten days, was of widespread distribution over trunk, limbs and face, and morbilliform in character. There was great loss of weight and strength during the fever, but recovery was rapid after the fall of temperature. He was discharged from hospital, cured, on June 11. The Weil-Felix test gave a positive reaction on June 12 (Kingsbury).

CASE VII.—A.T., male, aged thirty-three years, was living at Mossman and engaged in planting sugar cane. His illness began on May 21 with headache and fever. He was admitted to hospital on May 23. The temperature was 37·5° C. (99·6° F.), the pulse rate was 80. He complained of intense headache, particularly over the frontal region, and of pains in the limbs. The face was flushed and the conjunctivæ were congested. There was no rash. The temperature rose in "staircase" fashion during the next three days. There was considerable prostration. A widespread morbilliform rash appeared on the second day after admission. The spleen was not palpable. The glands of the neck were enlarged. The fever began to fall from the seventeenth day after admission and was back to normal on the nineteenth day. There was slight cough for two days towards the end of the fever. The Weil-Felix test gave a positive reaction (Kingsbury) on June 11.

CASE VIII.—G.G., male, aged forty-eight years, was engaged in scrub clearing near Tully. His illness began on May 28, 1935, with headache, shivers and vomiting. He rapidly became worse and was admitted to hospital, was very ill, and the "typhoid state" developed. On June 13 improvement began, and now (June 21) he is convalescing satisfactorily. The Weil-Felix test gave a positive reaction on June 19, 1935.

Table I illustrates the increasing titre obtained with tests on successive samples of blood, and the occurrence of rash and enlarged lymph glands.

The Technique Used in the Agglutination Tests.

The serum dilutions were prepared from 1 in 10 to 1 in 320 with 0·85% saline solution by the drop method in Dreyer's tubes.

The emulsions used were prepared from eighteen-hour agar slope cultures, the media being supplied by the Commonwealth Serum Laboratories, Melbourne.

The emulsions were prepared in 0·85% saline solution and standardized by the opacity test to 2,000 million per cubic centimetre. An amount of emulsion equal to the amount of diluted serum was added to each tube. The tubes were set in the water-bath at 37° C. and the final reading was made at the end of two hours. The sera that agglutinated to 1/640 were retested and taken to their full titre. Controls on the emulsions were used, and in addition tests were made, using the sera of ten normal healthy individuals; ten cases of diagnosed disease, including one convalescent lobar pneumonia and one puerperal sapræmia, were also used. No agglutination higher than 1/20 was found in any of the control tests.

In the case of positive tests the titre was recorded from the tube of highest dilution in which complete agglutination occurred.

The cultures used were subcultures of *Bacillus proteus* X 19, Kingsbury and Warsaw strains, received from the Lister Institute, London.

Discussion.

The cases at present recorded are proved beyond question to be endemic typhus. One of us (A.M.L.) is satisfied that practically all of the hundreds of cases of "coastal fever" he has encountered during fifteen years' practice in Cairns have been similar in nature to those described. The differences noted between individual cases, in different periods of the year and in different years are satisfactorily explained by the wide variation in clinical types found in the present series.

Dr. M. L. Unwin, Medical Superintendent of the Tully District Hospital, has informed one of us (R.Y.M.) that he has attended many hundreds of cases of "coastal fever" in and around Tully during the past seven years. He had decided on clinical evidence that his cases were endemic typhus and had completed a report which is awaiting further serological confirmation for publication.

Dr. D. C. C. Sword, who practised in Mossman from March, 1929, to April, 1934, and treated in that time 336 cases of "Mossman fever", has discussed with us the cases of "Mossman fever" quoted in these notes. He agrees that his cases were of the same nature as those now occurring.

An analysis of the records of the Cairns Laboratory since its opening in November, 1928, shows that there have been two main factors which have militated against the demonstration of positive reactions to the Weil-Felix test in the past, namely, unsuitable samples of blood serum and inadequate testing. In the first place the samples of blood tested for agglutination have been mainly collected early in the disease; retests have been infrequent.

In the second place, it was found in June, 1934, that suitable emulsions had not been regularly used in routine Weil-Felix tests. In June and early July, 1934, two positive tests (Kingsbury strain) were obtained with freshly prepared emulsions, where the old emulsions previously in use gave completely negative results. Further investigations at that time, however, were concentrated on abortive attempts at demonstrating the fevers occurring north of Tully as forms of leptospirosis.

We are now finding, with daily subculture of the strains of *Bacillus proteus* in use, that the agglutinability of the cultures is rapidly increasing. For example, a serum tested on June 10, 1935, gave a titre of one in forty (Kingsbury) with that day's emulsion. When tested on June 20, 1935, with the emulsions prepared that day, the titre was 1/640, Kingsbury.

It is confidently anticipated that with repeated agglutination tests in future cases of fever, abundant proof of the claims made in this contribution will be forthcoming.

Acknowledgements.

We are indebted to Dr. M. L. Unwin, of Tully, and Dr. H. S. Harper, of Mossman, for their ready cooperation and provision of clinical data, and to Mr. J. S. Whyte, biochemist, for his assistance in the laboratory work.

TABLE I.

Case Number.	Date of Onset.	Rash.	Enlarged Lymph Glands.	Agglutination Tests.[1]			
I	6/5/35	+	−	13/5/35 1/640 W.	20/5/35 1/640 W.	—	—
II	15/5/35	−	−	27/5/35 1/320 K.	—	—	—
III	26/5/35	+++	−	4/6/35 K.W. negative.	10/6/35 1/640 K.	1/1280 K.	—
IV	2/6/35	−	−	10/6/35 K.W. negative.	17/6/35 1/2560 K.	—	—
V	28/5/35	+	+	10/6/35 K.W. negative.	14/6/35 1/640 K.	—	—
VI	19/5/35	+	+	1/6/35 K.W. negative.	8/6/35 1/80 K.	12/6/35 1/640 K.	19/6/35 1/1280 K.
VII	21/5/35	+	++	1/6/35 K.W. negative.	12/6/35 1/640 K.	20/6/35 1/1280 K.	—
VIII	28/5/35	+++	+	12/6/35 1/80 K.	20/6/35 1/2560 K.	—	—

K = Kingsbury strain; W = Warsaw strain.

Post-Scriptum.

The term endemic typhus has been used in this paper to accord with current Australian usage in applying this term to all fevers of the typhus group other than epidemic louse-borne typhus. Since the paper was prepared for publication an additional sixteen cases have been diagnosed and confirmed by positive reactions to the Weil-Felix test, *Bacillus proteus* X 19, Kingsbury (eight from Cairns, one from Mossman, one from Innisfail, six from Tully). The "positive" sera of Cases III, V, VII and VIII have been check tested with heated emulsions of *Bacillus proteus* X 19, *proteus* X Warsaw, and *proteus* X Kingsbury. All gave positive reactions to the Weil-Felix test with *Bacillus proteus* X Kingsbury only (titres above one in three hundred) after three hours in water bath at 52° C. The positive serum of Case I gave a positive reaction to the Weil-Felix test with *Bacillus proteus* X 19 and Warsaw only.

Reports of Cases.

TWO CASES OF XERODERMA PIGMENTOSUM OCCURRING IN THE SAME FAMILY.

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Honorary Assistant Physician for Diseases of the Skin, Royal Prince Alfred Hospital; Honorary Physician for Diseases of the Skin, New South Wales Masonic Hospital.

THE two patients to be described exhibit at the present time most of the typical features of *xeroderma pigmentosum*. As will be seen from the following histories, the condition commenced in each instance with an erythematous dermatitis of the exposed surfaces and with a marked sensitivity to light. Although these factors are acknowledged forerunners of the disease, the special feature of interest is a muscular flexure of the left wrist, which occurred in both patients. This is accompanied by partial loss of function of the left hand and fingers in both instances. There are eleven children in the family, the two affected children being respectively fourth and seventh in age. The eighth child, according to the father, is slightly affected. No history of intermarriage among the father's or mother's antecedents could be elicited.

The case histories are as follows:

E. O'C. is a female, aged fourteen years. The father states that at the age of three months the child awoke one morning with her face swollen and red. This condition gradually subsided and was accompanied by some crusting and weeping. Ever since then her face, hands and forearms have been affected in a similar manner on prolonged exposure to daylight, particularly bright sunlight. This has been most noticeable in summer, and in windy weather when the child was outdoors. At the age of three the left wrist was noticed to assume a flexed position and has continued to become more flexed until the present date. Progressive loss of the use of the fingers of the left hand has accompanied the flexing of the wrist.

During the last few years the exposed parts of the legs have shown similar symptoms to the face and hands, but have improved since long black stockings have been worn.

On examination an erythemato-squamous appearance of the skin, interspersed with whitish, atrophic, parchment-like areas and irregular brownish pigmentation, forms the main characteristic of the eruption. The general appearance is sharply demarcated and is limited to the exposed surfaces on the neck, arms and legs, but is less pronounced in the latter region. Several areas of commencing keratosis are present on the face, being most noticeable around the mouth and chin. Rhagades are present at the angles of the mouth. On the dorsum of the left hand is a keratotic, verrucose lesion, suggesting a commencing carcinoma. Apart from this, no other definitely malignant transformations are present. Mild photophobia is also apparent. The left wrist shows a degree of flexion which produces almost a right angle between the hand and forearm. The wrist cannot be straightened by force, con-

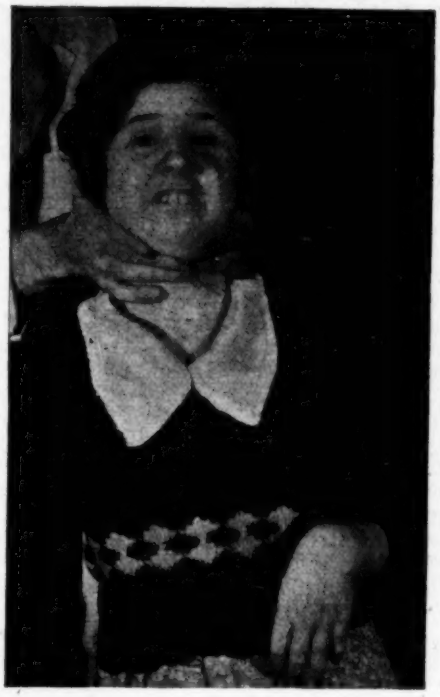

FIGURE I.

Photograph of the girl, showing the flexure of the left wrist.

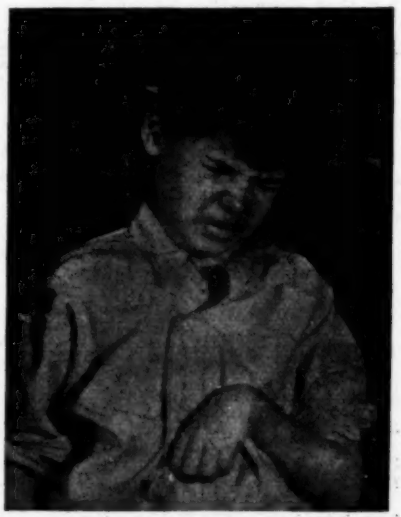

FIGURE II.

Photograph of the boy, showing the flexure of the left wrist. Note the evidence of photophobia.

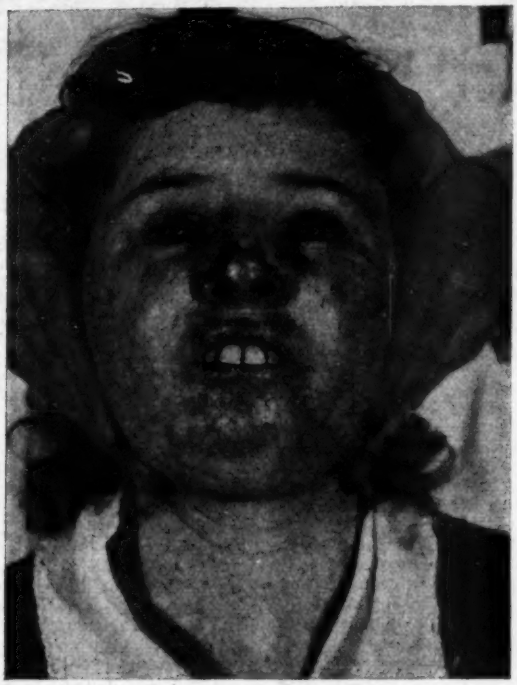

FIGURE III.

Photograph of the girl, showing involvement of the face, neck and exposed part of the chest. Note rhagades around the angles of the mouth, and areas of early keratosis.

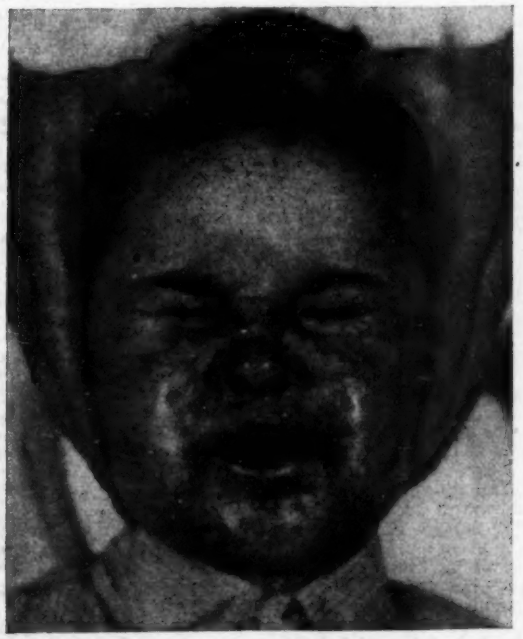

FIGURE IV.

Photograph of the boy, showing symptoms of marked photophobia, the general appearance of the skin of the face as described, and the area of denuded infiltration on the lower lip.

siderable pain being caused when an attempt is made to do so. There is partial loss of control of the fingers and hand.

Neither the Wassermann nor the Kline test yielded a positive reaction.

A differential blood count gave the following information:

Red cells, per cubic millimetre	4,670,000
Hæmoglobin value	81%
Colour index	0·88
(No abnormal forms were seen.)	
Leucocytes, per cubic millimetre	10,300
Neutrophile cells	67%
Lymphocytes	28%
Eosinophile cells	3%
Monocytes	2%

A light cloud of albumin was present on examination of the urine, but no traces of hæmatoporphyrin or acetone were detected.

No bony abnormality of the wrist was observed on X ray examination.

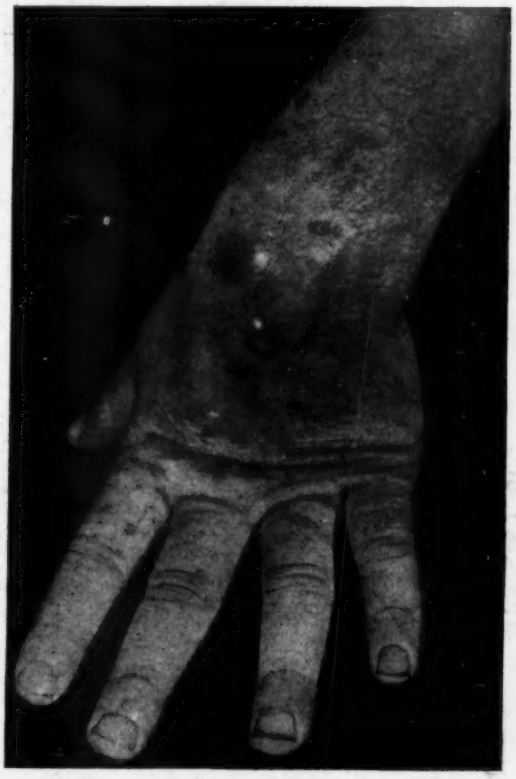

FIGURE V.

Photograph of the left hand of the girl, showing a keratotic verrucose lesion on the dorsum, suggesting a commencing carcinoma.

K. O'C. is a male, aged eight years. The father states that when the child was six months old a reddish appearance was manifest on his face. This disappeared and no further trouble was noticed until the child was twelve months old. At this time, after a day's play in particularly bright sunlight, he broke out in a rash similar to that affecting his sister. The rash affected the exposed surfaces and has remained until the present date, with temporary improvement in winter and aggravation in summer. At the age of two years the left wrist began to assume a flexed position, which has gradually become more marked.

On examination the same erythemato-squamous appearance as on the first patient is present, interspersed with

white, atrophic, parchment-like areas of skin, varying shades of brownish pigmentation, and some commencing keratoses. There is an area of denuded infiltration in the centre of the lower lip, suggesting a carcinomatous change. The legs are more affected than those of the sister. (The sister now wears long black stockings.)

Flexture of the left wrist, almost forming a right angle between the hand and forearm, similar to that of his sister, is present. There is the same partial loss of finger and hand control. Marked photophobia is present in this case. In neither instance is there any noticeable loss of sensation in the left hand.

FIGURE VI.
Photograph of the boy's legs, showing involvement of the exposed surfaces.

Both the Wassermann and Kline tests failed to yield a positive reaction.

A differential blood count yielded the following information:

Red cells, per cubic millimetre	4,150,000
Hæmoglobin value	64%
Colour index	0·78
(No abnormal forms were seen.)	
Leucocytes, per cubic millimetre	10,800
Neutrophile cells	41%
Lymphocytes	44%
Eosinophile cells	4%
Monocytes	11%

No traces of albumin, hæmatoporphyrin or acetone were found in the urine.

X ray examination revealed no bony abnormality of the wrist.

The examination by a psychiatrist placed the standard of intelligence of both children in a very low grade category.

Reviews.

A BOOK OF LECTURES FOR NURSES.

TECHNICAL education is curiously slow in adopting progressive ideas; while great activity has been shown in improving the methods of educating the very young, the older student is often left to his own devices. The truth of this generality may be seen in a comparison of modern techniques in kindergarten methods and those used in some university departments, even allowing for the differences in age and attainments of the pupils. So it is that the trained nurse has only in the last few years in this country been given much thought as regards the methods by which, in a few brief years, she becomes a highly skilled technician. Now, happily, the importance of preliminary training schools for nurses is recognized in most large hospitals, and the work of the tutor sister in the nurse's early training is greatly assisted by a book such as the "Lectures for Nurses" by Sister G. N. Burbidge.[1]

The greater part of this book consists of a brief presentation of the subjects studied by the probationer nurse during the period of her preliminary training. Thus anatomy and physiology, elementary hygiene, bandaging, and general nursing methods are dealt with, and in addition there is a concluding section which summarizes the information necessary for a complete knowledge of the general nursing procedures as applied by more senior nurses. It is evident that such a book must of necessity be a book of reference, since most of the subjects can only be taught practically, but it must be invaluable for any nurse to have a clear description of all official and standard methods. Little excursions into medical history add much to the point and interest of the book, though the reference to Saint Anthony's fire, on page 122, as being synonymous with gangrene due to rye-fungus invites criticism. The strictly medical information is not always impeccably correct; thus the attributing of uræmia to "poisoning substances such as urea", though perhaps a simple approximation for a nurse, is a misstatement. The section on vitamins might also be written so as to be more nearly accurate and at the same time useful to a nurse. But these criticisms only show how extremely hard it is to describe medical matters to nurses in clear and yet accurate terms; only those who attempt this difficult business can appreciate it.

The technical methods described are complete, reliable and simple; all training school teachers have their own ideas, and small divergences from individual custom may be found by various readers. It will be noticed that the usual rules are given for the calculation of doses of drugs from tablets of given strength *et cetera*; we always look at these things in amazement. Why should it be necessary for the nurse to rely upon a memorized rule, when it is much simpler and more reliable for her to understand the underlying principle? It is, of course, necessary to give examples in text books, but most medical practitioners would hope never to be given a hypodermic injection by a nurse who has to remember to "invert fraction of drug on hand, multiply by dose required, and multiply by dilution of drug at hand" and so forth.

These remarks are general and in no way are intended to reflect on this book, which is without doubt an excellent one of its kind. It is compact, clear and authoritative, and even (in fact one might say especially) in training schools where there is no preliminary school it will be found just what is wanted by student nurses. It is to be hoped that it will help many nurses to a clearer understanding and a more practical application of their work.

[1] "Lectures for Nurses", by G. N. Burbidge, S.R.N.; 1935. Sydney: The Australasian Medical Publishing Company, Limited. Crown 8vo., pp. 327. Price: 7s. 6d. net.

The Medical Journal of Australia

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APATHY, INTEREST AND VISION.

That the whole face of medical practice has changed during the last few years is recognized by all medical practitioners; even the recent graduate cannot fail to see the constant changes that are taking place. Expressed in the broadest way, medical practice may be described as becoming less individual and more collective. The term collective may be applied not only to preventive health measures aimed at groups of people in the community or at the community as a whole, but also to such aspects of practice as those connected with the modern hospital and all that goes with it. Treatment of an individual who is the subject of an infection will always remain the province of the medical practitioner — the world, however standardized, however brave and new it may become, is never likely to see standardization either of infective agents or of the body tissues attacked by them. A great deal, perhaps most, of the change in medical practice is the result of advance in medical knowledge, but sight must not be lost of the effects of so-called modern civilization—the altered economic conditions of the peoples of the world, their closer relationship with one another as a result of developments of modern transport, and their desire to have, in sickness as well as in health, what they have been taught to regard as the best.

This is not the occasion for a discussion on how far the public is justified in its aims and aspirations and in its demands on the medical profession. The point is that changes are occurring, developments are still taking place, and the medical profession cannot shut its eyes to them. The tradition of the medical profession demands that it shall take the lead, even at the price of its own extinction, in conservation of the health of the community; and legitimate pride in its status will not allow it to submit to exploitation. But the medical profession cannot be progressive and watchful if its members are apathetic. Medical practitioners are not apathetic about the conduct of their practices, but this cannot always be said of them in a corporate sense. At a recent medical dinner held at Sydney more than one speaker deplored the lack of interest taken in the affairs of the Local Medical Association that was holding the function, and in British Medical Association matters. As far as the scientific meetings of the Branch are concerned, the speakers were undoubtedly right in what they said, for many of the most important Branch discussions are held before a mere handful of people. In matters affecting the public welfare we do not believe that the members of the Branches are wholly apathetic. When things appear to be going well members do not feel the need for showing much enthusiasm, and this is perhaps characteristic of human nature. The members of the Branches have not shown themselves lacking in energy when a call to service in the interests of public health has arisen, nor have they been lacking in cohesion when inroads on their legitimate rights have been attempted.

In offering what may be called an apologia for the placidity of members of the Branches we do not suggest that the placidity should be undisturbed. Ideally every Branch member should be fired with zeal in science and with energy in medical politics. This will happen only when they have vision for the future. Solomon, the fount of much wisdom, said many hundreds of years ago that where there is no

vision the people perish. These words have been used to adorn many a tale and to point many a moral; in the present instance they are apt. Before the rank and file of the profession become endowed with this most excellent quality it must be manifest in their leaders. No one will deny that the far-seeing eye has in the past led the Branches to pursue courses of the greatest wisdom. But the eye should be kept trained on the needs of the future, whilst the resources of the present are marshalled to subserve them. Too often in recent times self-seeking, pride, jealousy and personal spite, and sometimes stupidity, have stepped in and frustrated or at least hindered a project that none but a warped mind could oppose. The voluntary mental myope is usually obvious; the members of the Branches should disregard him; Branch councils should not allow him to assert himself; he should be left to revolve around his own importance. Until apathy is turned to interest and interest takes to itself vision the medical profession of Australia in the ever-changing scenes of practice will not do its duty to the public either in preventive medicine or in the collective treatment of disease; it will not do its duty to itself.

Current Comment.

IMMUNIZATION TO DIPHTHERIA BY A SINGLE INJECTION.

Dr. Hilda Bull has recently drawn attention in this journal to the need for immunization to diphtheria in Australia. She pointed out that there are about 15,000 cases of diphtheria reported per year, and that 400 to 500 deaths occur annually, but she remarked that the experience of Melbourne during State-wide epidemics of the disease had been very encouraging, even with the limited amount of preventive work that could be carried out. Dr. K. Gardner Kerr has also contributed to these pages an analysis of the results of diphtheria immunization in Bendigo, also strongly in favour of greater extension of such work. Dr. Bull considers that it is better to use a bland material given in divided doses than to antagonize patients and their parents by uncomfortable reactions. If, however, a single injection method is perfected, it will doubtless make a much wider appeal. The question then is: Are we to advocate the toxin-antitoxin mixture, which is effective as an immunizing agent and with a low percentage of troublesome reactions; a toxin-antitoxin suspension, which is more potent and even less reactive, but more costly; or anatoxin? The last named, otherwise known as formol toxoid or alum toxoid, according to its means of preparation, is of superior potency to toxin-antitoxin, and with care does not give rise to undue reactions. It is therefore of great interest to know if it may be relied upon to produce a satisfactory degree of immunity with a single injection and if its use is free from unpleasant side-effects. C. N. Leach, C. Jensen and G. Poch have collaborated in investigating this question, using the resources of the Rockefeller Foundation in America, the State Serum Institute in Denmark, and the Local Health Department of Eisenstadt, Austria.[1]

Following on the historic observations of Roux and Yersin that the addition of metallic salts to broth containing diphtheria toxin caused the formation of precipitates which contained antigen in varying quantity, many attempts have been made to fix the antigen first by adsorption to some non-specific substance, and, secondly, in the local site of injection, so as to produce greater antibody formation. Alum has been one of the most successful materials used, but if a fairly high proportion is employed it is found that an indurated lump is produced at the place of the injection, and this may take a long time to disperse, and in a few instances even cause the formation of an abscess. The material used in the present work was the alum hydroxide toxoid, which appears to have the double advantages of securing a high degree of absorption with purified toxoid and being at the same time relatively unirritating. One of these authors has already carried out similar work on 6,000 Danish children, and in the present instance the area chosen was a restricted one in Austria, a small community in Mattersburg, where there has been a steady and relatively heavy incidence of diphtheria. Five hundred and fifty-three children in all were treated, and the toxoid was administered in doses of two cubic centimetres at the inferior angle of the scapula. Only about 12% of the children showed a local or general reaction, and it was found that such reactions were twice as frequent among children who gave a past history of diphtheria. This supports the view that reactions are due to hypersensitiveness to the specific diphtheria antigen. The Danish experiments, carried out on a population presumably less heavily infected, gave a much lower incidence of reactions. But such reactions as occurred were not severe, and in no case was an abscess caused. The degree of immunity attained was not tested by observing changes, if any, in the response to the Schick test, but by titrating the antitoxin content of the serum in a series of cases. Tests were made prior to the injections and again after one month. These revealed a very constant increase in the antitoxin titre, which was in the majority of cases very considerable. The greatest degrees of increase were observed in those children whose blood serum showed

[1] *The Journal of Laboratory and Clinical Medicine*, February, 1935.

a perceptible amount of antitoxin at the outset, thus giving a parallel to the experience gained in the immunization of horses in the manufacture of commercial antitoxin. No evidence of any negative phase was found.

Though the practical results are difficult to assess in a small series over a short period, it was found that in over a year from the time of the treatment no cases of diphtheria occurred among the 553 inoculated children, whereas among a control group of 175 children of the same age groups there were seven cases of clinical diphtheria. Careful records are being kept so that the progress of all the children may be followed. Prophylaxis of infectious disease is a matter of the closest concern to all the community, and none is more interested in this than the general practitioner. He is constantly being appealed to in this regard, but it is first necessary to give him weapons that are potent against the bacterial invader, but harmless to the patient. Every practitioner undertaking the medical care of children should interest himself in this matter, for diphtheria is still a serious disease, especially in cases of infection by the *gravis* type of organism, against which ordinary antitoxin may be found by no means a certain cure.

MALARIA AND HÆMOGLOBINURIA.

THE study of malaria has been facilitated to some extent by the discovery that *Plasmodium knowlesi* is pathogenic to the monkey *Silenus rhesus*. *Plasmodium knowlesi* is a natural parasite of some monkeys. It causes little apparent disturbance to the health of *Silenus radiatus* or *Silenus irus*; but when transmitted experimentally to *Silenus rhesus* it produces a dangerous, often fatal illness. If the infection is very heavy, hæmoglobinuria may occur. A study of this hæmoglobinuria may be the means of increasing our knowledge of blackwater fever in man. At present little more is known of the ætiology of this dangerous disease than that it is always preceded by malaria. In human malaria there is a tendency to an increase in the numbers of large mononuclear cells in the blood. Presumably these cells are part of the body's defences against the plasmodia or their products; and if blackwater fever is purely a sequel or complication of malaria, they may be concerned in its prevention. K. V. Krishnan has recently recorded the results of a series of observations on the reticulo-endothelial system in malarial hæmoglobinuria of monkeys.[1] In the first part of the paper he points out that, as reticulo-endothelial cells are concerned in the removal of damaged and dead red cells and free hæmoglobin from the blood, a study of the changes in them, before, during and after a paroxysm of hæmoglobinuria, might reveal valuable information concerning their rôle in the prevention or production of hæmoglobinuria. Of 25 rhesus monkeys infected with *Plasmodium knowlesi*, 14 suffered from hæmoglobinuria. The intensity of the infection was very high and was roughly the same in all cases. The difference in the numbers of reticulo-endothelial cells in the two groups was striking: in the monkeys with hæmoglobinuria the percentage varied from 2% to 7% of the total number of leucocytes; in the others, from 11% to 30%. Krishnan remarks that in a number of instances it was possible to predict the onset of hæmoglobinuria merely from a knowledge of the blood picture. Seven of the hæmoglobinuric monkeys were treated, two recovering; of those without hæmoglobinuria, two of six untreated and four of five treated recovered. Improvement in the sick animal's condition in each case was associated with a sharp rise in the numbers of reticulo-endothelial cells in the peripheral blood. In some cases in which death occurred the count decreased during the course of the illness; in others it rose slightly, perhaps to fall away again before death; in others again it rose considerably. In the last mentioned cases Krishnan thinks that the anæmia was the cause of death. A particularly interesting observation was that in monkeys with hæmoglobinuria and monkeys that died without hæmoglobinuria the activity of the reticulo-endothelial cells seemed to be depressed; when supra-vital staining was employed, they ingested less neutral red than normal cells. Krishnan concludes that when the reticulo-endothelial system is depressed sudden severe hæmolysis, as in malaria, results in hæmoglobinuria. When the reticulo-endothelial system is functioning properly the cells are able to dispose of free hæmoglobin and to prevent hæmoglobinuria.

The second part of the paper is the work of Krishnan and B. M. Ghosh; it deals with the relation of the spleen to hæmoglobinuria. Several workers have shown that splenectomy renders monkeys more susceptible to malarial infection. Krishnan noted that even *irus* and *radiatus* monkeys frequently suffered from hæmoglobinuria when infected with *Plasmodium knowlesi* after splenectomy. Krishnan and Ghosh believe that these effects of splenectomy are due to depression of the reticulo-endothelial system. With this in mind they performed splenectomy on 56 monkeys and infected them and 62 controls with *Plasmodium knowlesi*. They observed that the incidence of hæmoglobinuria was much higher among monkeys without spleens, and that no *radiatus* or *irus* monkey was affected unless its spleen had been removed.

The mere fact of splenic enlargement suggests the importance of the reticulo-endothelial system in malaria and blackwater fever. Grave depression of the reticulo-endothelial system may occur in man, possibly even comparable with that produced by splenectomy. Krishnan and Ghosh have gathered most valuable data as a basis for further research. At the same time it must be remembered that there are differences between monkey hæmoglobinuria and blackwater fever; for example, as Krishnan and Ghosh themselves point out: the cause of hæmolysis in monkeys is apparently the intense malarial infection; the cause of the hæmolysis in man is unknown.

[1] *The Indian Medical Gazette*, April, 1935

Abstracts from Current Medical Literature.

MEDICINE.

Treatment of Acute Lobar Pneumonia.

J. W. LINNELL (*The Practitioner*, January, 1935), discussing the treatment of acute lobar pneumonia, advises consideration of the actual cause of death of its victims. He gives reasons for rejecting the views that death results from toxic myocarditis or from failure of the vasomotor centre. Death may be due to pneumococcal septicæmia in a few cases, but in the rest it results from peripheral circulatory failure. The minute blood vessels lose their contractility much as in histamine shock, and the condition has been termed "toxæmic shock". The first essentials of treatment are rest and good nursing. The rest should be absolute in that enemata are preferable to aperients, the patient should not be allowed to turn himself, and examinations after the diagnosis has been arrived at should be avoided. Abundance of fluid is essential—five to six pints in the twenty-four hours—and as glucose is the most easily absorbed energy-producing food, it may be sufficient, if the patient has abundant home-made lemonade, to depend wholly on the glucose content as a food. As the serum chloride is low it is reasonable to supply common salt, for example, ten grammes daily. Oxygen, properly given, should be administered from the first. Strychnine and camphor in therapeutic doses have no action on the circulation and their stimulation of the nervous system may be harmful. Pituitrin and adrenaline, which theoretically should be useful, have in the presence of toxæmia little or no action on the capillaries. There is some difference of opinion as to the value of digitalis; the author does not use it in this condition. Morphine is of the greatest value in every stage of the disease, provided capillary bronchitis is not present and the typhoid state has not supervened. He has never seen anything but good follow its free use. Antipneumococcic serum is held to reduce mortality very appreciably in Type I and to some extent in Type II infections, yet "one of the best known English workers" found the fatality rate in Type I slightly increased with serum.

Silicosis.

P. HEFFERNAN (*Tubercle*, June, 1935) endeavours to give an adequate answer to the vexed question: What is silicosis? It has long been known that the condition of the lung subjected to the influence of dust, whether healthy or already damaged or infected, greatly modifies the form of the fibrosis thus produced. There are in practice a number of types of pulmonary fibrosis, beginning with simple silicosis and merging into fibrotic conditions in which dust, siliceous or other, plays a minor part or no part at all. Diseased lungs are dust traps, and the finding of dust in such lungs is no proof that the disease was caused by the dust. Nevertheless the author maintains that silicosis is a unique pathological entity due to a unique pathological process. He therefore answers the question in the following postulates: (1) "Silicosis" is a nodular fibrosis of the lungs, produced by the inhalation of siliceous dust. (2) The interaction which produces "silicosis" is electro-chemical in nature, and is typically caused by "free silica", for example, quartz, when in a state of electro-chemical activity, acting upon certain cells of the pulmonary tissues. (3) Silica is active electro-chemically (*a*) at the surfaces of the particles of freshly powdered silica (aerosol) and (*b*) in freshly made hydrosols. (4) There is reason to suspect that certain mineral silicates, for example, asbestos, when freshly pulverized into fine powder, are also electro-chemically active at the surfaces of the particles and capable of acting in a similar manner to powdered quartz, but to a much more limited extent, setting silica, so to speak, partially "free" at the surfaces. (What is set "free" is, of course, the electro-chemical energy of the silicon tetrahedra at the new surfaces.) (5) The properties of the silicates mentioned in (3) and (4) depend upon their stereo-chemical crystal-structure. (6) The harmful properties of the dusts referred to above are considerably modified by the presence of certain other dusts. (7) There is reason to believe that aqueous "solutions" of some silicates are "systems" containing, when freshly made, active silica hydrosol. These postulates involve the acceptance of the electro-chemical activity of crystals and colloids found in silica and silicates rather than the solubility of the latter as the chief cause of silicosis.

Uræmia.

D.-M. GOMEZ (*La Presse Médicale*, February 9, 1935) describes the action of certain extracts of renal cortex on urea retention. Intramuscular and subcutaneous injection of a cortical extract (three or four cubic centimetres daily for five to seven days) was practised in uræmic hypertensive subjects in whom the blood urea content was greater than 40 centigrammes per litre. In the majority of 37 patients so treated the blood urea diminished within twenty-four hours and continued for six months at a lower level than before the treatment. An exception occurred in those patients whose blood urea was above 70 centigrammes per litre before treatment; in these patients the blood urea did not fall. Administration of renal cortex extract by mouth was without effect. In thirty patients it was shown that the blood pressure fell coincidently with the fall in blood urea following subcutaneous or intramuscular injection of kidney cortex extract. The patients' symptoms improved as the blood urea and blood pressure diminished.

Pulmonary Tuberculosis in Adolescence.

P. F. ARMAND-DELILLE (*Tubercle*, May, 1935) states that there is general agreement today that the development of pulmonary tuberculosis in adolescence indicates local reinfection of an organism primarily infected in infancy. He gives three main pathological types: splenopneumonia or epituberculosis, a pneumonic form, and the fibro-caseous or ulcerative type found in adult life. The first usually commences without obvious cause, though sometimes it follows an acute infection; it is characterized by fever of the typhoid type. Symptoms may suggest pleurisy, but no fluid is found. The X ray shadow is characteristic, suggesting a large area of consolidation; and it may remain unaltered for months. The temperature usually settles in one month and the child recovers. This disease is to be regarded as a manifestation of allergy. The second, the pneumonic type, commences much as does lobar pneumonia, and signs are similar. But the temperature is more irregular and no crisis occurs. Râles become abundant, cough increases and loss of weight is rapid. Radiographically, in the area of consolidation an irregular punched-out cavity may be seen. Immediate artificial pneumothorax is the only means of arresting the rapid progress; the patient's resistance is lost and death occurs otherwise in a few months. The third, or adult, type of the disease has a more insidious onset. Usually fatigue, anorexia and loss of weight are presenting symptoms; cough and hæmoptysis are not common. Pneumothorax and sanatorium treatment should be instituted as soon as possible, when the prognosis is reasonably good. The author maintains that, contrary to the opinion of earlier clinicians that pulmonary tuberculosis in adolescence is always very severe and rarely heals, early diagnosis, followed by artificial pneumothorax and subsequent sanatorium treatment, leads to cure in a great number of cases.

Specific Gravity of the Urine of Renal Impairment.

G. E. F. SUTTON (*The Practitioner*, February, 1935), in a contribution on hyperpiesia, draws attention to the value of the specific gravity estimation of the urine, which will discover slight degrees of impairment of the renal function not shown by urea tests. The presence in the urine of a

trace of albumin, together with a few casts, is not necessarily indicative of nephritis; but in uncomplicated cases of hypertension there should be no nocturia; and in patients on a normal diet the specific gravity of the urine should not be low and should show variation if examined every two hours throughout the day. The specific gravity test should be performed as follows. For twenty-four hours after breakfast on a given morning the patient should be allowed neither liquids nor liquid foods. During the last twelve hours of this period the urine is collected and the specific gravity ascertained. Under these conditions the specific gravity should be at least 1026. In terminal nephritis it is usually found to be under 1010. It is important that the estimation should be made more than once, as, for some unknown reason, a normal subject will occasionally excrete a urine of low specific gravity. The simplicity of the test may be the reason why its great value is not recognized.

Premature Cardiac Contractions.

J. B. CARTER AND E. F. TRAUT (*The American Journal of the Medical Sciences*, February, 1935) discuss the uses of quinidine and strychnine in the treatment of premature contractions. Twenty-one patients who had cardiac extrasystoles were treated by quinidine sulphate, 0·18 gramme (three grains), and strychnine sulphate, 2·2 milligrammes (one-thirtieth of a grain), thrice daily; 17 patients improved in that the heart became more regular and caused fewer symptoms, such as giddiness, palpitation and syncope. Quinidine and strychnine given separately had little effect. To one patient 0·6 gramme (ten grains) of quinidine sulphate were given thrice daily for five days. No ill-effects were observed in these patients. The authors discuss the dangers of quinidine treatment, but consider that they have been exaggerated.

The Treatment of Malaria.

JOHN R. BLAZE AND A. T. W. SIMEONS (*The Indian Medical Gazette*, April, 1935) describe their experiences of the treatment of malaria by "Atebrin musonate". "Atebrin musonate" is a yellow powder, readily soluble in water; it is supplied in ampoules, each containing 0·125 gramme. The dose recommended by the manufacturers is the contents of one to three ampoules for intramuscular injection and one ampoule for intravenous injection. The authors record 21 cases, giving brief histories illustrated with charts. They found that the intramuscular injection of "Atebrin musonate" in therapeutic doses gave rise to no toxic or unpleasant symptoms. A single injection of 0·375 gramme of the drug sometimes had a remarkable effect, causing a rapid subsidence of symptoms; but there was usually a recrudescence within a few days. Two injections of 0·375 gramme each, with an interval of twenty-four hours, caused disappearance of the fever in forty-eight hours and disappearance of benign tertian or malignant tertian trophozoites from the peripheral blood within a maximum period of four days. There was no recurrence of fever in any case during the period of observation. Crescents were apparently unaffected by the drug. The authors express the opinion that "Atebrin musonate" is a drug worthy of further investigation. They admit that the period of observation in their series of cases was not long enough to permit comparison of the results with those obtained by quinine therapy and the oral administration of "Atebrin".

Malaria.

R. N. CHOPRA, S. K. GANGULI AND A. C. ROY (*The Indian Medical Gazette*, February, 1935) report the results of a series of observations on the quinine concentration and parasite count in the blood of monkeys infected with *Plasmodium knowlesi*. Quinine was administered intramuscularly or intravenously, and the quinine concentration and parasite count were determined simultaneously at fixed intervals. No relationship was found between the quinine concentration in the blood and the numbers of parasites. There was no decrease in the numbers of parasites nor any evidence of degeneration of the parasites when the quinine concentration was at its highest. In several instances the parasites increased in number immediately after the injection of quinine. The infection was not controlled until two or three injections at intervals of twenty-four hours had been given, irrespective of the concentration of quinine in the blood. The authors remark that if quinine has a directly lethal action on the plasmodia of malaria, the object should be to produce a high concentration of quinine in the blood as rapidly as possible; but the evidence obtained from their experiments "does not warrant the view that a high concentration of quinine will have an immediate and direct lethal action on the malarial parasites". They suggest that the action of quinine is "synergistic to other defensive mechanisms set up in the body". In their experiments they observed that once the number of parasites approximated to one million per cubic millimetre of blood, death occurred, no matter how much quinine was given.

Latent Sepsis.

W. H. OGILVIE (*The Practitioner*, February, 1935) summarizes the manifestations of latent sepsis, pointing out yearly increase of the incidence of lesions which are presumably caused by sub-infections with non-specific organisms or by the distant action of the toxins of such organisms which have become established in some part of the body without causing any severe focal reaction. To latent sepsis may be attributed the disabilities following injuries, and thrombosis and embolism after operations, which rarely occur before the age of thirty. Long after all clinical signs of an inflammatory condition have disappeared the causative bacteria may persist, although encapsulated in dense non-vascular connective tissue or bone. Streptococci are particularly prone to survive. The presence of living organisms is shown by the reaction resulting from the injection of a foreign protein, which will usually stir a focus to activity. A focus, even if active to the extent of producing fever and leucocytosis, may from its position escape thorough clinical examination. Examples of such hidden foci are small abscesses in the perirenal fat or the interlobular septa of the lungs. The streptococci are the most important of the organisms in latent septic foci. Organisms liberated from foci are typically arrested in the sparse capillaries of non-vascular structures and give rise to round cell infiltration followed by fibrosis. The toxins liberated into the blood stream affect organs well supplied with blood and cause degeneration in the kidneys, spleen, liver, heart and ductless glands. Manifestations of latent sepsis may be general, giving rise to loss of energy and a feeling of ill-health; subacute or chronic conditions in the fibrous tissues, such as painful heels, sciatica, or nodules on tendons and periostitis; articular lesions, as subacute or chronic arthritis; cardiovascular lesions, such as endocarditis and arterial degeneration; and in the nervous system peripheral neuritis and degeneration of the spinal cord. It must in any given case be determined that latent sepsis is the cause; the search may be lengthy, onerous and fruitless. In many cases the association of the disease with the presence of focal sepsis is so constant that immediate search may be justified. The following preliminary observations may be recorded: the temperature, especially taken when the feeling of malaise is present; the white cell count, which, though it may be from 9,000 to 12,000 per cubic millimetre, may show relatively numerous young cells; and the determination of the sedimentation rate of the red cells. These three examinations are extremely helpful only if positive results are obtained; a negative result is of little importance. Bacteriological examination should be made from the lesion under observation, from the blood and from the urine. The focus may be found in the teeth, tonsils or accessory sinuses, and less commonly in the middle ear, the lungs and pleura, in the gall-bladder and appendix, in the prostate and the uterus, in the fat deposits of the body, particularly the perirenal fat, in the long bones and in the scars of wounds or accidents.

British Medical Association News.

SCIENTIFIC.

A MEETING OF THE SECTION OF MEDICINE OF THE NEW SOUTH WALES BRANCH OF THE BRITISH MEDICAL ASSOCIATION was held at the Robert H. Todd Assembly Hall, British Medical Association House, 135, Macquarie Street, Sydney, on June 13, 1935, DR. O. A. A. DIETHELM in the chair.

Agranulocytosis.

DR. A. S. WALKER read a paper entitled: "Agranulocytosis" (see page 133).

DR. G. C. WILLCOCKS said that he had seen three or four patients suffering from agranulocytosis. One of these, a woman whom Dr. Shipton had seen with him, had recovered after the administration of liver extract. Dr. Willcocks was not prepared to say whether the liver extract had had any influence on the progress of the disease in this case. Another patient, a child, aged six years, had been admitted to the Royal Alexandra Hospital for Children with severe anæmia and a temperature of 39·4° C. (103° F.). The child had been ill for some weeks, but had become better, and then, shortly before admission, had become feverish. Typhoid fever had been suspected. The leucocytes had numbered 800 and the red blood cells 2,950,000 per cubic millimetre; no neutrophile cells had been seen. The throat had been inflamed. In ten days the red cell count had dropped to 1,275,000 per cubic millimetre, and by this time the leucocytes had increased in number to 10,000 per cubic millimetre, with 75% neutrophile cells. The faucial and buccal lesions had resembled the lesions that Dr. Willcocks had previously observed in agranulocytic angina. Treatment had consisted in the administration of liver extract; the response, ten days after the commencement of treatment, had coincided with the onset of pleurisy and pneumonia. Dr. Anderson thought that the occurrence of an abscess at a site of injection of liver extract had had some effect in drawing leucocytes into the blood. Dr. Willcocks thought the case was typical of agranulocytosis. He assumed that the anæmia had been due to erythrocyte destruction.

DR. E. A. SHIPTON expressed her thanks to Dr. Walker for the paper, which she had found very interesting. She wished to touch on several points that Dr. Walker had not mentioned.

Dr. Shipton believed that the adult patient referred to by Dr. Willcocks, and who had been first seen by her in a typical acute attack, had later consulted Dr. Diethelm; this patient had recovered temporarily under treatment by liver extract; her red blood cell count had never been below 3,500,000 per cubic millimetre. Another patient that Dr. Shipton had seen with Dr. Willcocks had failed to respond to either "Pentnucleotide" or liver extract, and had died in three days with a final leucocyte count of 800 per cubic millimetre.

Dr. Shipton mentioned the opinions of Frank given in Schittenhelm's text book of hæmatology, where the syndrome described by Schultz was regarded as a variation of *aleukia hæmorrhagica* or panmyelophthisis. Frank thought it unwise at present to take a narrow view of the disease. One writer had expressed the opinion that a diagnosis of agranulocytosis could not be made unless the red blood cells were intact.

Dr. Shipton went on to say that the increase in the numbers of mononuclear cells was apparent only in the majority of cases. Nevertheless a few cases had been reported in which the mononuclear cell count had been actually high.

There had been a suggestion that a disturbance of certain endocrine glands might be a factor in the causation of granulopenia. Dr. Shipton thought that the suprarenal glands might have an influence. Corry and Britten had shown that these glands (especially the cortical parts) had an important influence on the polymorphonuclear cells. Removal of the glands caused a decrease of the polymorphonuclear cells; but injection of cortical extract produced a recovery in the number of these cells. A case of lymphadenoma had been reported in which no granulocytes could be found in the blood or lymphadenomatous deposits; at autopsy it had been found that the suprarenal glands were greatly affected with lymphadenomatous tissue. In the French literature several cases had been reported in which the ovaries, thyreoid and posterior part of the pituitary had been sclerosed, the anterior part of the pituitary remaining intact. Dr. Shipton thought it might be worth while to treat patients with injections of suprarenal cortical extract.

The question of whether granulopenia occurred secondarily to sepsis was important. Dr. Shipton said that she had seen granulopenia develop in streptococcal septicæmia and in pneumonia. Feér in 1926 had reported over 3,000 cases of angina and sepsis, including one case of pyelitis in which the leucocyte count had fallen to 300 per cubic millimetre. Dr. Shipton believed that the granulopenia in these cases had been secondary to sepsis. She suggested that the suprarenal glands might have been affected.

Dr. Shipton stressed the importance of careful *post mortem* examination in hospital practice as a means to discovering the cause of granulopenia. This was usually impossible in private practice.

Dr. Shipton went on to say that the diagnosis of the condition was not usually difficult to the hæmatologist. Glandular fever might be accompanied by a low leucocyte count; but here the result of the Hanganatzin-Deicher test for heterophile antibodies was always positive. Careful hæmatological studies—daily if necessary—would eliminate leuchæmia.

DR. J. H. HALLIDAY said that he had attended a patient, a man in the early fifties, who had sustained an abrasion of a finger while shearing. Some days later the patient had had a rigor and a painful swelling had appeared in the axilla. A few days later examination of the blood had revealed granulopenia. The mass in the axilla had increased in size and had been opened, when a large quantity of serum, but no pus, had escaped; a large necrotic mass, presumably portion of the subscapularis muscle, had been removed. Blood transfusion had been done before the operation, and the affected area in the axilla had healed completely. A pathologist at the time had been unable to decide whether the condition was one of granulopenia or so-called aleuchæmic leuchæmia, though finally inclining to the latter diagnosis. Later the patient had developed recurring indurated swellings on the surface of the tongue and also on the arms. These had been painful, but had disappeared after varying periods without any pus formation. Blood transfusion had been performed on several occasions and "Pentnucleotide" had been administered without success. After a few weeks the patient had developed pneumonia and pleurisy. Transfusion of blood had been repeated thereafter without avail and the patient had died.

DR. C. H. SHEARMAN said that the patient under the care of Dr. Lorimer Dods, mentioned by Dr. Walker, had presented several features of interest. He had been a male—and among males the disease was relatively uncommon—and, although he had been very ill for many days, had eventually made a complete recovery. Dr. Shearman had carried out several hæmatological and bacteriological investigations in this case. At one stage the leucopenia had been so severe that only 450 white cells per cubic millimetre could be counted, and none of these had been of the granular type. As fusiform bacilli and spirilla had been present in large numbers in the necrotic lesions in the mouth, two injections of "Novarsenobillon" had been given, and Professor Lambie had been of the opinion that some response had occurred to this form of treatment. The patient had been given blood transfusion on two occasions. The day following the first transfusion there had been a slight increase in the number of leucocytes; but the next day the number had decreased. The second transfusion had then been given and had been followed next day by an increase in the leucocyte count, though no granular cells could be seen. It had not been

until the onset of the pneumonic condition that any granular cells had appeared in the blood; with their appearance the total leucocyte count had rapidly increased.

DR. A. W. HOLMES À COURT congratulated Dr. Walker on his very thorough exposition of the difficult subject of agranulocytosis. He doubted whether the disease was so rare in this community as it appeared to be in England, judging by published statistics, having himself seen at least six cases in the past four years. One of these cases had already been referred to by Dr. Walker in quoting particulars furnished by Dr. Lorimer Dods. This patient had failed to respond to transfusion of whole blood or to irradiation, but had eventually recovered after developing lobar pneumonia, which had induced a healthy leucocytic response. Dr. Holmes à Court thought that there must be some factor other than failure of maturation of the granular cells to account for the granulopenia in the circulating blood. In one patient who had received a transfusion of 1,000 cubic centimetres of whole blood, an examination of the blood immediately afterwards had shown that the granular cells had actually further decreased in number; this observation appeared to suggest that there was active destruction of granular cells.

He inquired whether any members present had seen good results from "Pentnucleotide", as in his own experience it had been disappointing. If he remembered correctly, when the original report of the Harvard Neucleotide Commission had appeared in *The American Journal of the Medical Sciences*, the claim had been made that 74% of cases had been satisfactory. Subsequent reports seemed to indicate much less optimistic figures.

DR. O. A. A. DIETHELM, the Chairman, said that, on behalf of the Section of Medicine, he wished to thank Dr. Walker for his admirable paper and to pay a tribute to his learned discussion of the subject of agranulocytosis.

In regard to the question of sepsis as a possible cause of the disease, Dr. Diethelm mentioned a female patient, aged thirty-five years, who had injured her scalp during a voyage from Adelaide. The patient had not been well prior to the commencement of the voyage; also there had been a history of an infection of the arm twelve months previously. At the time of Dr. Diethelm's examination of the patient the wound in the scalp had healed; but there had been some surrounding cellulitis and tenderness and swelling on both sides of the neck. Enlargement of the spleen, together with fever (a temperature of 40·5° C.), had suggested the possibility of enteric fever; but there had been no reaction to the Widal test. There had been an agranulocytic type of blood picture, the leucocytes numbering 1,600 per cubic millimetre, of which 18% were neutrophile cells, 80% lymphocytes and 2% monocytes. The patient had been very ill. Soon after her admission to hospital stomatitis had occurred and the enlarged glands on each side of her neck had become inflamed, and in the course of a few days a tremendous boggy swelling had appeared in the neck. Sir John McKelvey had incised this swelling without finding pus. Examination of smears had revealed pus cells and staphylococci; *Staphylococcus aureus* had been cultured. The leucocyte count had now increased to 6,400 per cubic millimetre (65% neutrophile cells, 33% lymphocytes and 2% monocytes). Incision of a swelling on the other side of the neck by Sir John McKelvey had again failed to reveal pus. The patient's fever had gradually subsided, her symptoms had improved, the swelling in her neck had disappeared, and she had completely recovered.

Dr. Diethelm also mentioned the case of a woman, aged fifty-seven years, who had had neutropenia with a possible preexisting leucopenia associated with depressed bone marrow function from toxæmia. The patient had complained of exhaustion and had suffered from boils, some of which had been opened without draining frank pus. All her teeth had been removed for pyorrhœa. There had been tonsillar remnants, oozing pus. The patient had suffered from sciatica and neuritis, which had been relieved after the removal of the teeth. The tonsils had been treated with surgical diathermy on several occasions. When first seen by Dr. Diethelm the patient's leucocytes had numbered 1,800 per cubic millimetre, 98% being lymphocytes and 2% neutrophile cells, all cells being normal in appearance. There had been a mild hypochromic anæmia. No organisms had been cultured from the blood. The leucocyte count had gradually increased to 3,600 per cubic millimetre (61% neutrophile cells); diathermy had then been applied to her tonsils again, and in two weeks the number of leucocytes had fallen to 1,900 per cubic millimetre (22% neutrophile cells). During the period of improvement many band forms had been seen. After this relapse she had gradually improved again. On two occasions a remarkable regression had also followed the administration of "Novalgin", the patient on the first occasion complaining of lethargy and tiredness; on the second occasion the fall in the numbers of leucocytes had not been so severe.

In regard to ætiology, Dr. Diethelm said that it seemed fairly evident that patients with an agranulocytic blood picture, similarly to those with so-called agranulocytic angina, were persons whose bone marrow reacted differently to bacterial infection than most people's. It could hardly be argued that this peculiarity in reaction was an inborn permanent condition; for there were cases in which the patient had reacted with the usual polymorphonuclear increase to one infection and had had an agranulocytic reaction to another. It was a moot question whether the bone marrow condition preceded the local infection or followed it. If it was assumed to precede it—and certainly in some cases the patient was ill before the appearance of local lesions—then the condition of the bone marrow had to be accounted for. Something, perhaps some toxin, damaged the bone marrow and paralysed its ability to form granulocytes. It was natural to think of this action as a toxic one, from analogy with the known effects of chemical substances, such as benzol, thorium and arsphenamine, on the bone marrow. On the other hand, there was evidence in some cases that in the early stages of the infection there was still granulocyte formation and that the agranulocytosis became more and more pronounced as the infection progressed; this suggested the infection as the cause of the lesion in the bone marrow. Again, in some cases of recovery the damage to the bone marrow was not permanent and irreparable. In the present state of knowledge the question must be left open.

Dr. Diethelm concluded his remarks by again expressing his thanks to Dr. Walker.

Dr. Walker, in reply, expressed his thanks for his hearers' forbearance and for the discussion.

Dr. Willcocks had referred to the improvement of a patient when pneumonia had supervened, and of another when an abscess had occurred. Dr. Walker pointed out that granular cells must be present to form an abscess and that the improvement had occurred, not so much because of the abscess, but because granular cells had for some reason appeared. He was unable to give any satisfactory explanation for this; in other cases recovery had occurred without pus formation. Dr. Willcocks had also referred to the anæmia and the destruction of the red cells. Dr. Walker said that in the bone marrow there were three classes of tissue: one for the production of red cells, one for leucocytes and one for platelets. Could it be assumed that a disease that affected one class of tissue only would invariably be so selective? In agranulocytosis this was usually so; but there might be unknown causes that could produce an affection of the other parts of the marrow. Such cases were hard to classify. The same question was involved in Dr. Shipton's remarks about hæmorrhages in granulopenia. Dr. Shipton's views were after his own heart, for she had voiced a philosophic outlook. With regard to hæmorrhages, he remarked that it was difficult to know whether they were due to granulopenia or not, as apparently there was here a deficiency in platelets also. In these cases it was not easy to draw a line of distinction; but was not this the story right through medicine? The observer had to be very careful what cases he put in any category. Dr. Shipton had mentioned the monocyte count in granulopenia; Dr. Walker said that he had meant to convey that the increase was usually relative only. Dr. Shipton and Dr. Diethelm had discussed

possible causes of the disease; Dr. Walker believed that there was a variety of causes.

In reply to Dr. Holmes à Court, Dr. Walker said that he was interested to hear confirmation of the observations of Plum, who had reported cases in which the granulocytes had actually decreased in number after blood transfusion. With regard to "Pentnucleotide", he said he had no personal proof of its value; the only cases in which he had used it so far had turned out not to be true cases of granulopenia. The later results of this drug had been rather disappointing; but Dr. Walker felt that no possible remedy should be neglected.

Dr. Diethelm had mentioned sepsis as a possible cause of granulopenia; the truth was that no one fully understood the causes. Dr. Walker went on to say that the person who had derived most benefit from his paper was himself. He stressed the importance of keeping a watch for granulopenia and investigating and following up cases as carefully as possible. The same care should be exercised in the performance of *post mortem* examinations. In conclusion he said that he was glad that his pathologist colleagues had dealt with him so generously.

A MEETING OF THE VICTORIAN BRANCH OF THE BRITISH MEDICAL ASSOCIATION was held at the Austin Hospital for Chronic Diseases, Heidelberg, Victoria, on April 17, 1935. The meeting took the form of a series of clinical demonstrations by members of the honorary staff.

Surgical Tuberculosis.

DR. H. C. TRUMBLE gave a comprehensive and informative demonstration of his methods of treating the subjects of chronic tuberculosis of the spine and of the hip joint. The demonstration included treated patients, their case histories and their skiagrams arranged in chronological order. Dr. Trumble does not use metal splints of any description for these patients, but at the commencement of treatment, on each occasion, he makes a plaster bed on which the patient is rested until the condition becomes quiescent. When he deems it necessary he operates to secure fixation by means of grafts of transplanted living bone. He plans the operation to avoid the actual focus of disease. He uses a modification of the Albee operation for lower spinal conditions, but prefers the Hibbs type of operation for lesions of the thoracic spine. He has designed a special operation for the hip joint, in which the graft is placed under the joint from the upper portion of the shaft of the femur to the seat-weight-bearing bone of the ischium. He claims that these grafts support the joint and prevent adduction. One skiagram in particular demonstrated how the graft has grown almost to the size and strength of the shaft of the femur, and from its appearance there could be no question that it was transmitting body weight.

Dr. Trumble emphasized the importance of regular monthly search for *Bacillus tuberculosis* in the urine of these patients, and stated that it was found on isolated occasions sometimes, especially in the case of those lying in bed for months. He felt that on such occasions a bacillæmia of a transient nature occurred, and said that further evidence was required before a diagnosis of tuberculosis of the urinary tract could be substantiated.

Later in the evening Dr. Trumble made a plaster bed with eight-ounce scrim (hessian) reinforcement similar to those described by him in *The British Journal of Surgery*, Volume XIX, Number 14, 1931.

DR. E. T. CATO and DR. C. A. M. RENOU also demonstrated some of the good results that they had obtained in the treatment of tuberculosis of the spine by means of bone grafts, and showed two patients who were very strong and well fourteen months and seventeen months respectively after operation. Another patient shown by them was able to walk and to run without disability after excision of the knee joint for tuberculous disease.

Tube Grafts in Rodent Ulcer.

Dr. Cato and Dr. Renou also demonstrated the use of tube grafts in closing the deficiency after diathermy for rodent ulceration of the face.

Radiograms of the Spinal Column.

DR. E. R. CRISP demonstrated a series of films illustrating various lesions of the spinal column. The films shown included examples of tuberculous osteomyelitis of early, moderately advanced and gross degree, traumatic changes, herniation of the *nucleus pulposus*, partial collapse of one vertebral body, complete lateral dislocation of the column, and spondylolisthesis. Other films represented the appearances of the involvement of vertebral bodies by Hodgkin's disease, by osteoclastic and osteoplastic metastases, and by hæmangioma of thecal vessels. The changes typical of Paget's disease were compared and contrasted with those due to metastases from prostatic malignant disease.

Results of X Ray Therapy.

DR. ALAN MACKAY, junior, showed two patients and the films of two others to whom he had given deep X ray therapy. The first patient was a man, aged forty-one years, who had had œdema of the ankles on exertion for ten years, with increasing lassitude and dyspnœa. His condition was diagnosed as myeloid leuchæmia early in 1934 and he was admitted to hospital on March 20, 1934, with hydrothorax, ascites and considerable enlargement of the liver and of the spleen. At this stage the white cells were estimated to be 437,000 and the red cells 4,610,000 per cubic millimetre, and the colour index was 0·65. Only small X ray treatments were given, owing to his weak condition, but by June 25 the white cell count had fallen to 32,000 and he was up and about. The œdema had disappeared and the spleen was barely palpable. During September he was given a second course of treatment on account of an exacerbation, and the response to treatment was quite definite, but by January 17, 1935, the lower edge of his spleen had come down below the umbilicus and the white cell count had risen to 204,000 per cubic millimetre. A third course of treatment was instituted, and on February 14 the spleen was almost of normal size and the number of white cells had fallen to 15,000 per cubic millimetre. At that date he was discharged from hospital, free of symptoms, having put on over a stone in weight. On readmission on the day of the meeting his spleen was enlarged again and the white cell count had risen once more to 183,000 per cubic millimetre.

Dr. Mackay's second patient was a woman, aged forty-seven years, who was admitted to hospital in July, 1934, with Hodgkin's disease. She had had a swelling of the right side of the neck for eighteen months and subsequently glandular enlargement had occurred in the left axilla and on the left side of the neck. Latterly she had complained of dyspnœa on exertion, and at the time of admission a large left hydrothorax was present, but no glands were palpable in the abdomen or in the groins. On a number of occasions the left side of the chest was aspirated and deep therapy was given. The glands subsided after repeated treatments and the hydrothorax resolved. In March, 1935, the glands in the left side of the neck, left axilla and left subpectoral area became enlarged again and œdema of the left breast occurred. A further course of treatment was commenced and the glands became small again; the breast had been reduced to about half its previous size and had become very little larger than the right breast.

Of the skiagrams exhibited by Dr. Mackay, the first series were those of the chest of a man, aged forty-one years, who in 1929 had had a gland removed from the left axilla which had been diagnosed elsewhere as affected by Hodgkin's disease. He was admitted to hospital in September, 1933, in a moribund condition and was very dyspnœic, with irregular bulging of the ribs, massive infiltration of both pectoral regions, and with gross enlargement of the liver. At this stage a film showed a large ovoid mass projecting half way across both lung fields from the mediastinum, with an associated right hydro-

thorax. Therapy was given with great improvement, and films showed rapid retrogression of the mediastinal tumour one week after treatment. He was readmitted to hospital on several occasions with severe dyspnœa, cyanosis and tachycardia, and each time his symptoms cleared up about one week after treatment. In a recent letter he stated that he was perfectly well and free of symptoms. The diagnosis was lymphosarcoma of the mediastinum.

The second series of films showed a pathological intertrochanteric fracture through a metastasis in the right femur of a woman, aged forty years, who in January, 1933, at the Melbourne Hospital had had radium inserted into a carcinoma of the left breast. The first film, taken on July 7, 1933, showed a large area of destruction of the right femur involving both trochanters, with an associated fracture through the thin cortex. Deep therapy was given to the area, and a film, taken on July 7, 1934, showed firm bony union of the fracture, with reorganization of the trabeculæ and no demonstrable evidence of the secondary deposit. Now she had a local recurrence in the breast.

Dr. Mackay also presented a man, aged thirty years, who was admitted to the sanatorium ward on May 5, 1934, with pulmonary tuberculosis, which had improved steadily under routine treatment. Four years ago he noticed for the first time that there was a small nodule on his left upper eyelid. This nodule was removed by his private medical attendant, but it recurred and, on his admission to hospital, it was about the size of the nail of a little finger. It was removed under local anæsthesia in September, 1934, and after microscopic examination Dr. R. D. Wright reported that it was "an adenocarcinoma with cells resembling those of sebaceous or Meibomian glands". A radium plaque, with heavy filtration, was applied to the area and only a small, barely palpable scar was now present. The sight of the eye was unaffected.

Malignant Disease of the Pharynx and of the Larynx.

DR. THOMAS MILLAR demonstrated a series of cases of inoperable carcinoma of the pharynx and of the larynx which were being treated by deep X ray therapy. He made a special appeal to general practitioners for assistance in the early diagnosis of these cases and presented each visitor with a copy of the following notes, under the heading "Points for General Practitioners Regarding Cancer of the Larynx":

> Laryngologists are largely dependent on general practitioners for the early diagnosis and successful treatment of cancer of the larynx. Persistent hoarseness and local discomfort are the only diagnostic leads to early diagnosis. Dysphagia, pain and dyspnœa only occur in advanced cases. Therefore don't treat hoarseness in a patient of over forty for more than the first week or two without a laryngeal examination. Remember cancer inside the larynx is the most favourable of any cancer in the body. Of 200 cases the duration of hoarseness was: under six months, 54; over six months and under one year, 46; over one year, 76. Of 200 cases, 144 commenced as favourable growths and were thus at some time diagnosable and curable. Only 50 were seen in time for removal by laryngofissure.

Physical Therapy.

DR. FRANK MAY presented a woman, the subject of tuberculous peritonitis, whom he was treating by means of ultra-violet rays, and discussed the technique.

Dr. May's other patient was undergoing a form of treatment which was a novelty in Melbourne. She had disseminated sclerosis and her temperature was kept above normal by means of a heated bed and a diathermy machine. Dr. May said that the artificial fever therapy required close attention by a medical practitioner, who decided frequently whether the temperature should be advanced or retarded, according to the manner in which the treatment was being borne by the patient. Dr. May presented a number of the charts of patients treated in this way and pointed out that in one case the temperature had risen to 42·1° C. (107·8° F.). In a general way those patients with disseminated sclerosis tended to have more rapid pulse rates (approximately 150 per minute) than the subjects of general paralysis of the insane (approximately 110 per minute) while they were undergoing this form of treatment.

Dr. May stated that he was not yet able to give more than a preliminary report of the results of treatment, but said that he would analyse his results next year.

Pulmonary Tuberculosis.

DR. J. BELL FERGUSON showed two patients upon whom thoracoplasty had been performed, and six others who had been submitted to phrenic evulsion. These patients had been selected to illustrate the rapidity with which demonstrable cavitation could occur, and the equivalent rapidity with which a cavity might disappear after the appropriate operation had been performed. Dr. Ferguson presented some films to demonstrate these facts. In one case only six weeks had elapsed between the taking of one film showing a small focus in the lower lobe, and of another film of the same patient, in which could be seen quite a large cavity in the position which had before been occupied by the small focus.

Another set of films showed very clearly how the affected part of the lung collapsed first and expanded last with artificial pneumothorax. After phrenic evulsion in one case the paralysed side of the diaphragm took up an unusually high position and a cavity at the apex of the upper lobe closed in a most gratifying manner.

Dr. Bell Ferguson considered that in some cases the effect of phrenic evulsion was unnecessarily severe, and instanced an example of hæmoptysis following this procedure. He mentioned that by crushing the phrenic nerve immobility of the lung for some six months could be obtained, and he thought that in selected cases this time might suffice for a cure, which would, of course, be more satisfactory when the lung was able to function later in a normal manner. If the period of six months was not long enough, a further crushing might be feasible. He also discussed the advisability of phrenic resection in other cases as a procedure which, though equally effective, was less violent than evulsion.

Carcinoma of the Uterus.

DR. J. M. BUCHANAN showed four patients illustrative of various sequelæ of treated *carcinoma uteri*. The first was a woman in whom a *carcinoma cervicis*, Stage III, had been treated at the hospital eighteen months previously by radium and deep therapy. The local reaction had been excellent and she remained well for twelve months after treatment. Within the past six months, however, she had noted swellings in the left frontal area and girdle pains round the chest. Clinical investigation revealed that the pelvic area was satisfactory. Radiological examination showed the presence of extensive secondary involvement of the calvarium and collapse of the sixth thoracic vertebra. Deep X ray treatment to the frontal areas gave some symptomatic relief from headaches.

Dr. Buchanan's second patient had been treated by radon for *carcinoma cervicis*, Stage III (early), twenty-five months previously and had responded well until some three months prior to her readmission to hospital. She then complained of cough, dyspnœa and the expectoration of blood-stained sputum. Investigation resulted in the discovery of an abdominal tumour in the right iliac fossa, though the condition in the pelvis was satisfactory. The mass had no obvious relation to the original pelvic lesion and appeared to be a metastatic growth in the internal iliac group of lymphatic glands. X ray examination of the chest showed the presence of a large infiltrating tumour of the mediastinum involving the right lung to a considerable extent. Her general condition had deteriorated considerably in the past three weeks.

The third patient had been treated with radium for early *carcinoma cervicis* six years ago. After her original treatment she had been free of symptoms for five and a half years and had discontinued reporting periodically because

she was so well. At this time she experienced pain in the left leg and left iliac fossa, which progressed until recently there was considerable swelling in the left leg. Pelvic examination established the presence of a sloughing mass in the left side of the pelvis attached to the pelvic wall. The swelling of the left leg was due to lymphatic œdema. The long period of quiescence before recurrence was the feature of interest. As the International Standards recognized a symptomless interval of five years as a cure, Dr. Buchanan thought that this patient was a "cure", but her outlook at present was undoubtedly grave.

Dr. Buchanan's fourth patient had been under the care of Dr. Robert Fowler at the Alfred Hospital. She had been suffering from uterine hæmorrhage for which intrauterine radiation was undertaken six months ago. At this stage biopsy showed hypertrophied mucous membrane only. On account of an increase in the size of the uterus, vaginal hysterectomy was performed three months later. Microscopic examination of the specimen proved it to be an example of degenerating chorion epithelioma. Ten days after operation a vaginal nodule appeared, which was treated with radium interstitially. At that stage she was transferred to the Austin Hospital, where a course of deep X ray treatment was in progress. The nodule disappeared and she gave no reaction to the Aschheim-Zondek test. It would appear that her prospect for ultimate cure was good.

ANNUAL MEETING, MELBOURNE, 1935.

THE following is the programme of the meetings of the sections in connexion with the annual meeting of the British Medical Association to be held at Melbourne from September 9 to 13, 1935.

The following sections will meet on three days:

SECTION OF MEDICINE.

Office-Bearers.

President: The Right Honourable Lord Horder, K.C.V.O., D.C.L., M.D., F.R.C.P. (London).

Vice-Presidents: J. Crighton Bramwell, M.D., F.R.C.P. (Manchester), A. W. Holmes à Court, M.D., F.R.C.P. (Sydney), Professor C. G. Lambie, M.C., M.D., F.R.C.P. (Sydney), Sir James Purves-Stewart, K.C.M.G., C.B., M.D., F.R.C.P. (London).

Honorary Secretaries: S. O. Cowen, M.D. (12, Collins Street, Melbourne, C.1), J. G. E. Hayden, M.D., M.R.C.P. (55, Collins Street, Melbourne, C.1), J. C. Matthews, M.C., M.D., F.R.C.P. (Hazelacre, Downton, Wilts).

Programme.

Wednesday, September 11.

10 a.m.—Discussion, "Obesity, Ætiology and Metabolism", to be opened by Professor C. G. Lambie (Sydney), followed by Dr. J. H. Anderson (Ruthin Castle) ("The Treatment of Obesity") and Dr. E. H. Stokes (Sydney).

12 noon.—Occasional papers: Dr. A. Clarke Begg (Swansea), "Diabetic Gangrene"; Dr. S. O. Cowen (Melbourne), "Hæmolytic Jaundice, Pathogenesis and Treatment".

Thursday, September 12.

10 a.m.—Discussion, "The Differential Diagnosis and Treatment of Severe Anæmia", to be opened by Dr. J. C. Matthews (Downton), followed by Dr. J. H. Anderson (Ruthin Castle) ("The Treatment of Pernicious Anæmia") and Dr. C. T. C. de Crespigny (Adelaide), Dr. A. Clarke Begg (Swansea), Dr. Eva Shipton (Sydney), and Dr. Ian Wood (Melbourne).

12 noon.—Occasional paper: Dr. Crighton Bramwell (Manchester), "The Significance of 'Gallop' and Other Types of Triple Rhythm".

Friday, September 13.

Combined meeting with Section of Surgery. Discussion on thyreotoxicosis, to be opened by Lord Horder (London) and Sir Thomas Dunhill (London), followed by Professor Hercus (New Zealand), Dr. Hume Turnbull (Melbourne), Dr. A. W. Holmes à Court (Sydney), Sir Carrick Robertson (Auckland, New Zealand), Dr. Alan Newton (Melbourne).

SECTION OF SURGERY (INCLUDING UROLOGY).

Office-Bearers.

President: Sir Thomas Dunhill, K.C.V.O., C.M.G., M.D., F.R.A.C.S. (London).

Vice-Presidents: Clifford Morson, O.B.E., F.R.C.S. (London), Sir Henry Newland, C.B.E., D.S.O., M.S., F.R.A.C.S. (Adelaide), F. C. Pybus, M.S., F.R.C.S. (Newcastle-on-Tyne), Sir Carrick Robertson, M.B., F.R.C.S. (Auckland, New Zealand).

Honorary Secretaries: A. E. Coates, M.D., M.S. (3, Linda Crescent, Hawthorn, E.2, Victoria), H. C. Trumble, M.C., M.D., Ch.B., F.R.C.S. (19, Collins Street, Melbourne), Lambert C. Rogers, F.R.C.S., F.R.A.C.S., F.A.C.S. (British Post-Graduate Medical School, Hammersmith Hospital, Ducane Road, London, W.12).

Programme.

Wednesday, September 11.

10 a.m.—Discussion, "Hydatid Disease", to be opened by Professor H. R. Dew (Sydney) and followed by Dr. B. Kilvington (Melbourne), Dr. D. Carmalt-Jones (New Zealand), Dr. S. C. Fitzpatrick (Hamilton, Victoria), Dr. K. Fairley (Melbourne), Dr. K. S. Cross (Melbourne).

12 noon.—Discussion, "Surgery of the Pancreas", to be opened by Dr. Harold Upcott (Hull), followed by Dr. S. Finch (England) and Dr. B. Quick (Melbourne).

Thursday, September 12.

10 a.m.—Discussion, "Prostatectomy", to be opened by Dr. Clifford Morson (London), followed by Dr. A. H. Burgess (England), Dr. John Tait (Melbourne), Dr. Frank Macky (Auckland), Dr. G. H. Burnell (Adelaide).

12 noon.—Discussion, "Carcinoma of the Colon", to be opened by Sir Charles Gordon Watson (England), followed by Dr. F. C. Pybus (England), Dr. H. B. Devine (Melbourne), Dr. H. S. Souttar (England), and Dr. Victor Hurley (Melbourne).

Friday, September 13.

10 a.m. (combined meeting with Section of Medicine).—Discussion, "Thyreotoxicosis", to be opened by Lord Horder (England) and Sir Thomas Dunhill (London), followed by Professor C. E. Hercus (New Zealand), Dr. H. Hume Turnbull (Melbourne), Dr. A. W. Holmes à Court (Sydney), Sir Carrick Robertson (New Zealand), Dr. Alan Newton (Melbourne).

SECTION OF OBSTETRICS AND GYNÆCOLOGY.

Office-Bearers.

President: J. S. Fairbairn, F.R.C.S., F.R.C.P., P.C.O.G. (London).

Vice-Presidents: Professor R. Marshall Allan, M.C., M.D., F.R.C.S., F.R.A.C.S., F.C.O.G., F.A.C.S. (Melbourne), J. Bright Banister, M.D., F.R.C.S., F.R.C.P. (London), Ninian McI. Falkiner, M.D., F.R.C.P.I., F.C.O.G. (Dublin), Professor J. C. Windeyer, M.D., Ch.M., F.R.A.C.S., F.C.O.G. (Sydney).

Honorary Secretaries: Robert Fowler, O.B.E., V.D., M.D., F.R.C.S. (85, Spring Street, Melbourne, C.1), A. Roberta Donaldson, M.B., Ch.B. (89, Collins Street, Melbourne, C.1).

Programme.

Wednesday, September 11.

10 a.m.—Discussion, "The Present Position of Cæsarean Section in Obstetric Practice", to be opened by Dr. J. Bright Banister (London), followed by Professor J. B. Dawson (Dunedin, New Zealand), Dr. W. Ivon Hayes (Melbourne), Dr. H. A. Ridler (Sydney). Discussion, "Placenta Prævia", to be opened by Sir Comyns Berkeley (London), followed by Professor J. C. Windeyer (Sydney), Dr. A. M. Wilson (Melbourne).

Thursday, September 12.

10 a.m.—Discussion, "The Prevention and Prognosis of the Late Toxæmias of Pregnancy", to be opened by Dr. J. S. Fairbairn (London), followed by Dr. John S. Green (Melbourne) and Dr. F. Brown Craig (Sydney). Discussion, "The Remote Results of Puerperal Sepsis", to be opened by Sir Ewen Maclean, followed by Mr. Rupert Furber (Sydney).

Friday, September 13.

10 a.m.—Discussion, "The Ovarian Cycle and its Relationship to Endocrinology", to be opened by Dr. Ninian McI. Falkiner, followed by Dr. Bruce Mayes (Brisbane), Dr. F. A. Maguire (Sydney), Dr. R. F. Matters (Adelaide). Discussion, "Some Aspects of Heart Disease Complicating Pregnancy", to be opened by Dr. H. C. E. Donovan (Sydney), followed by British representatives.

RADIOLOGY AND RADIO-THERAPEUTICS.

Office-Bearers.

President: Dr. H. M. Moran, M.B., F.R.C.S., F.R.A.C.S. (Sydney).

Vice-Presidents: L. J. Clendinnen, M.B., B.S. (Melbourne), R. A. Gardner, M.B., D.M.R.E. (Cairo), Major D. B. McGrigor, O.B.E., M.B., D.M.R.E. (Frinton-on-Sea), D. I. R. Smith, M.B., B.S. (Western Australia).

Honorary Secretaries: F. G. Stephens, M.B., B.S. (12, Collins Street, Melbourne), A. J. G. Mackay, M.B., F.R.C.S., D.M.R.E. (Radiological Clinic, Parliament Place, East Melbourne, C.2).

Programme.

Wednesday, September 11.

10 a.m.—Discussion, "Radiation Treatment of Carcinoma of Breast", to be opened by Dr. H. M. Moran (Sydney), followed by Dr. R. A. Gardner (Cairo), Dr. R. Kaye Scott (Melbourne), Dr. S. Verco (South Australia). Discussion, "Radiation Treatment in Carcinoma of Tongue", to be opened by Dr. R. A. Gardner (Cairo), followed by Dr. H. M. Moran (Sydney) and Dr. L. J. Clendinnen (Melbourne).

Thursday, September 12.

10 a.m.—Discussion, "Radiological Diagnosis in Diseases of Lung", to be opened by Dr. J. G. Edwards (Sydney), followed by Dr. John O'Sullivan (Melbourne), Dr. B. L. W. Clarke (Brisbane). Discussion, "Some Notes on the Diagnosis of Bone Tumours", to be opened by Dr. H. R. Sear (Sydney), followed by Dr. Val. McDowall (Brisbane), Dr. Colin Macdonald (Melbourne), Dr. Howard Praagst (Melbourne).

Friday, September 13.

10 a.m.—Discussion, "Radiological Education", to be opened by Major D. B. McGrigor (Frinton-on-Sea), followed by Dr. K. S. Cross (Melbourne), Dr. K. Hallam (Melbourne). Discussion, "The Radiological Examination of Stomach and Duodenum", to be opened by Dr. K. S. Cross, followed by Dr. John O'Sullivan (Melbourne), Dr. H. A. McCoy (Adelaide), Dr. de Monchaux (Dunedin).

The following sections will meet on two days:

DISEASES OF CHILDREN.

Office-Bearers.

President: Robert Hutchison, LL.D., M.D., F.R.C.P. (London).

Vice-Presidents: E. H. M. Stephen, M.B. (Sydney), H. Douglas Stephens, M.D., M.S., F.R.A.C.S. (Melbourne), E. H. Williams (Dunedin), F. N. Le Messurier, D.S.O., M.B., B.S., M.D. (Adelaide).

Honorary Secretaries: J. G. Whitaker, M.D., M.S., F.R.C.S. (55, Collins Street, Melbourne, C.1), Ian J. Wood, M.D., M.R.C.P. (12, Collins Street, Melbourne).

Programme.

Wednesday, September 11.

10 a.m.—Discussion, "Hare Lip", to be opened by Dr. H. Douglas Stephens (Melbourne), followed by Sir Henry Newland. Discussion, "Infant Feeding", to be opened by Dr. H. Boyd Graham, followed by Dr. E. H. Williams (New Zealand), F. N. Le Messurier (Adelaide).

Friday, September 13.

10 a.m.—Discussion, "Pink Disease", to be opened by Dr. A. Jeffreys Wood (Melbourne) and Dr. Ian J. Wood (Melbourne), followed by Dr. R. Hutchison (London), Dr. Edgar Stephen (Sydney), Dr. S. F. McDonald (Brisbane). Discussion, "Intussusception", to be opened by Dr. P. L. Hipsley (Sydney), followed by Dr. Allan Vickers (Western Australia), Dr. H. C. Colville (Melbourne).

NEUROLOGY AND PSYCHOLOGICAL MEDICINE.

Office-Bearers.

President: Professor Edwin Bramwell, M.D., F.R.C.P., F.R.C.P. (Edinburgh).

Vice-Presidents: A. W. Campbell, M.D. (Sydney), Professor J. P. Lowson, M.D. (Brisbane), Professor F. Wood Jones, F.R.C.S., L.R.C.P., B.Sc. (Melbourne), Professor W. S. Dawson, B.Ch., M.D., M.R.C.P. (Sydney).

Honorary Secretaries: L. B. Cox, M.D., M.R.C.P. (37, Toorak Road, Malvern, Victoria), H. F. Maudsley, M.C., M.D., M.R.C.P., D.T.M. (8, Collins Street, Melbourne), J. K. Slater, M.B., F.R.C.P. (7, Walker Street, Edinburgh).

Programme.

Wednesday, September 11.

10 a.m.—Discussion, "Diagnosis, Prognosis and Treatment of Brain Tumours Fifty Years Ago and Now", to be opened by Professor Edwin Bramwell (Edinburgh), followed by Sir James Purves-Stewart (London), Professor Bouman (Amsterdam), Dr. H. M. Traquair (Edinburgh), Dr. A. W. Campbell (Sydney).

Friday, September 13.

10 a.m.—Discussion, "Psychoses of Adolescence", to be opened by Professor W. S. Dawson (Sydney), followed by Dr. A. W. Campbell (Sydney), Dr. Evan Jones (Sydney), Dr. J. K. Adey (Melbourne), Dr. C. Farran-Ridge (Melbourne).

OPHTHALMOLOGY.

Office-Bearers.

President: A. J. Ballantyne, M.D., F.R.F.P.S. (Glasgow).

Vice-Presidents: J. Lockhart Gibson, M.D., F.R.A.C.S. (Brisbane), F. G. Antill Pockley, M.B., M.S. (Sydney), H. M. Traquair, M.D., F.R.C.S. (Edinburgh), Lieutenant-Colonel R. E. Wright, C.I.E., I.M.S., B.A., M.D. (Madras).

Honorary Secretaries: J Ringland Anderson, M.C., M.B., B.Ch. (108, Collins Street, Melbourne), Max Yuille, M.B., F.R.C.S., D.O.M.S. (12, Collins Street, Melbourne), J. H. Doggart, M.D., F.R.C.S.E. (49, Wimpole Street, London, W.1).

Programme.

Thursday, September 12.

10 a.m.—Discussion, "Ætiology, Early Diagnosis and Medical Aspects of Glaucoma", to be opened by Dr. H. M. Traquair (Edinburgh), followed by Dr. A. J. Ballantyne (Glasgow), Dr. J. H. Doggart (London). Discussion, "Abnormal Retinal Correspondence and Other Hindrances to Fusion Training", to be opened by Dr. N. Bishop Harman (London) and Dr. T. a'B. Travers (Melbourne).

Friday, September 13.

10 a.m.—Discussion, "Cyclitis in Female Patients", to be opened by Dr. J. H. Doggart (London).

ORTHOPÆDICS.

Office-Bearers.

President: Professor E. W. Hey Groves, M.D., M.S., F.R.C.S. (Bristol).

Vice-Presidents: L. O. Betts, O.B.E., M.B., M.Ch. (Adelaide), S. T. Irwin, M.Ch., F.R.C.S. (Belfast), S. Alan S. Malkin, M.B., F.R.C.S. (54, The Ropewalk, Nottingham) (also acting as Home Secretary), J. Renfrew White, M.B., F.R.C.S. (Dunedin, New Zealand).

Honorary Secretary: Thomas King, M.D., F.R.C.S. (2, Collins Street, Melbourne).

Programme.

Thursday, September 12.

10 a.m.—Discussion, "Fractures of the Neck of the Femur", to be opened by Professor E. W. Hey Groves (Bristol), followed by Dr. S. T. Irwin (Belfast), Dr. Hoets (Sydney), Dr. Thos. King (Melbourne).

1 p.m.—Discussion, "Osteoarthritis of Knee and Hip", to be opened by Dr. J. Forbes Mackenzie (Melbourne) and Dr. S. A. S. Malkin (Nottingham).

Occasional papers: Dr. L. J. A. Parr (Sydney), Dr. D. W. L. Parker (Tasmania).

Friday, September 13.

10 a.m.—Discussion, "Fractures of the Spine", to be opened by Dr. S. T. Irwin (Belfast), followed by Dr. F. C. Pybus (Newcastle-on-Tyne) and Dr. J. B. Colquhoun (Melbourne).

11.30 a.m.—Discussion, "The Rôle of Physiotherapy in Treatment of Injuries in General and Orthopædic Practice", to be opened by Dr. E. B. M. Vance (Sydney), followed by Dr. S. A. S. Malkin (Nottingham) and Dr. C. W. B. Littlejohn (Melbourne) and Dr. L. Betts (Adelaide).

OTO-RHINO-LARYNGOLOGY.

Office-Bearers.

President: Francis Muecke, C.B.E., M.B., F.R.C.S. (London).

Vice-Presidents: J. Stoddart Barr, M.D., F.A.C.S. (Hobart, Tasmania), L. Graham Brown, M.C., M.D., F.R.C.S. (London), Douglas Guthrie, M.D., F.R.C.S. (Edinburgh) (also acting as Home Secretary), J. F. O'Malley, M.Ch., F.R.C.S. (London), W. N. Robertson, C.M.G., C.B.E., M.B., M.S., F.R.A.C.S. (Brisbane).

Honorary Secretaries: G. A. D. McArthur, M.D., F.R.A.C.S. (85, Spring Street, Melbourne, C.1), J. H. Shaw, M.B., F.R.C.S., D.L.O. (55, Collins Street, Melbourne), Douglas Guthrie, M.D., F.R.C.S. (4, Rothesay Place, Edinburgh).

Programme.

Wednesday, September 11.

10 a.m.—Discussion, "The Treatment of Maxillary Sinusitis", to be opened by Dr. J. F. O'Malley (London), followed by Dr. J. F. Woodburn (Sydney), Dr. Edgar Brown (Adelaide), Dr. Douglas Guthrie (Edinburgh).

Occasional papers: "Nasal Sinusitis in Children", by Dr. G. C. Scantlebury (Melbourne); "Nasal Neurosis or Allergies", by Dr. Hubert M. Jay (Adelaide).

Thursday, September 12.

10 a.m.—Discussion, "The Treatment of Chronic Suppurative Otitis Media", to be opened by Dr. L. Graham Brown (London), followed by Dr. Robt. Godsall (Sydney), Dr. H. J. Gray (Perth, Western Australia), Dr. J. Acomb (York).

Occasional papers: "Sphenoidal Sinusitis and the Pituitary Gland", by Dr. Clive M. Eadie (Melbourne); "Light Treatment in Laryngeal Tuberculosis", by Dr. T. G. Millar (Melbourne).

PATHOLOGY AND BACTERIOLOGY.

Office-Bearers.

President: Professor A. Murray Drennan, M.D., F.R.C.P. (Edinburgh).

Vice-Presidents: Professor J. B. Cleland, M.D., Ch.M. (Adelaide), W. Keith Inglis, M.D., M.S. (Killara, New South Wales), E. F. D'Ath, M.B., Ch.B. (Dunedin), W. J. Penfold, M.B., C.M. (Melbourne).

Honorary Secretaries: C. H. Kellaway, M.C., M.D., M.S., F.R.C.P. (Melbourne Hospital, Melbourne), Professor H. A. Woodruff, M.R.C.S., L.R.C.P. (48, Fellowes Street, Kew, E.4, Victoria).

Programme.

Wednesday, September 11.

10 a.m.—Discussion, "Calcification", to be opened by Dr. F. Hansman (Sydney), followed by Professor P. MacCallum (Melbourne), and Dr. Edgar King (Melbourne). Discussion, "The Pathology of Osseous Tissue", to be opened by Professor A. M. Drennan (Edinburgh), followed by Professor P. MacCallum (Melbourne), Dr. Keith Inglis (Killara, New South Wales), Dr. Edgar King (Melbourne) and Dr. R. Willis (Melbourne).

Occasional papers: "Leuchæmic Infiltrations", by Professor J. B. Cleland (Adelaide); "Neural Components in Teratomata", by Dr. R. Willis (Melbourne).

Thursday, September 12.

10 a.m.—Discussion, "Anaerobes in Disease", to be opened by Professor H. A. Woodruff (Melbourne), followed by Professor C. E. Hercus (Dunedin), Dr. W. J. Penfold (Melbourne), Dr. G. H. Oxer (Mt. Lawler), Dr. C. W. Adey (Melbourne). Discussion, "Problems in Virus Disease", to be opened by Dr. F. M. Burnet (Melbourne), followed by Professor H. K. Ward (Sydney), Dr. Lionel Bull (Melbourne), and Dr. E. V. Keogh (Melbourne).

Occasional papers: "Determination of Hæmoglobin as Globin Picrate", by Dr. A. Bolliger (Sydney).

PHARMACOLOGY, THERAPEUTICS AND ANÆSTHESIA.

Office-Bearers.

President: Sir William Willcox, K.C.I.E., C.B., C.M.G., M.D., F.R.C.P. (London).

Vice-Presidents: L. A. Ivan Maxwell, M.D. (Melbourne), Z. Mennell, M.B. (London), Professor Sydney Smith, M.D., F.R.C.P.E., F.R.C.S.E. (Edinburgh), G. R. Troup, M.B., M.R.C.P. (Perth, Western Australia).

Honorary Secretaries: Geoffrey Kaye, M.D. (14, Collins Street, Melbourne), B. L. Stanton, M.B., M.R.C.P. (Rotha, 95, Broadway, Camberwell, E.6, Victoria), E. Lewis Lilley, M.B., F.R.C.S. (Waterloo Gates, 86, New Walk, Leicester).

Programme.

Thursday, September 12.

10 a.m.—Discussion, "The Use and Abuse of Hypnotic Drugs", to be opened by Sir William Willcox (London). Discussion, "A Critical Survey of Urinary Antiseptics", to be opened by Dr. John Tait (Melbourne). Laboratory demonstration by Professor W. A. Osborne (Melbourne): A vaso-constrictor principle in the skin of the frog, *Hyla aurea*.

Friday, September 13.

10 a.m.—Discussion, "Premedication and Basal Narcosis", to be opened by Dr. F. W. Green (Melbourne). Discussion, "Gas Anæsthesia", to be opened by Dr. G. Kaye (Melbourne). Discussion, "The Position of Spinal Anæsthesia in Australia", to be opened by Dr. Leo Doyle (Melbourne).

PUBLIC MEDICINE (TUBERCULOSIS, INDUSTRIAL AND TROPICAL HYGIENE) AND INCLUDING THE HISTORY OF THE DEVELOPMENT OF MEDICINE IN AUSTRALIA.

Office-Bearers.

President: Sir Henry Gauvain, M.D., M.Ch., F.R.C.S. (Alton).

Vice-Presidents: Sir R. W. Cilento, M.D. (Brisbane), C. E. Hercus, D.S.O., M.B., Ch.B. (Dunedin, New Zealand), G. Carmichael Low, M.D., F.R.C.P. (London), C. M. Murray, D.S.O., M.A., B.Ch., M.R.C.S., L.R.C.P. (South Africa).

Honorary Secretaries: H. M. James, M.B., Ch.B. (22, Mayfield Avenue, Malvern, S.E.4, Victoria), F. R. Kerr, D.S.O., M.D., D.P.H. (27, Monomeith Avenue, Canterbury, E.7, Victoria), Professor R. H. Parry, M.D., M.R.C.P., D.P.H. (Bristol Health Offices, 40, Prince Street, Bristol).

Programme.

Wednesday, September 11.

10 a.m.—Discussion, "Incidence of Pleural Effusion in Artificial Pneumothorax, with Special Reference to Medical Treatment", to be opened by Dr. D. B. Rosenthal (Melbourne), followed by Dr. A. J. Collins (Sydney), Dr. D'Arcy Cowen (Adelaide), Dr. J. Bell Ferguson (Melbourne) and Dr. Bedford Elwell (Brisbane). Discussion, "The Surgical Treatment of Purulent Effusions in the Chest", to be opened by Dr. M. P. Susman (Sydney), followed by Dr. Allan Walker (Sydney), Dr. Henry Searby (Melbourne), Dr. Leo Doyle (Melbourne), Dr. G. Foreman (Melbourne).

Friday, September 13.

10 a.m. (combined with Section of Medical Sociology).—Discussion, "Racial Pressure Problems in Australia and Neighbourhood", to be opened by Sir R. W. Cilento (Brisbane), followed by Dr. E. Kaye Le Fleming (England), Sir James Barrett (Melbourne), Dr. D. Gifford Croll (Brisbane) and Rev. John Flynn (New South Wales). Discussion, "Tropical Medicine", to be opened by Dr. G. C. Low (London), followed by Dr. C. L. Park (Singapore). Discussion, "Weil's Disease", to be opened by Dr. T. J. Cotter (Queensland).

MEDICAL SOCIOLOGY.

Office-Bearers.

President: E. Kaye Le Fleming, M.D. (Wimborne).

Vice-Presidents: D. G. Croll, C.B.E., M.B. (Brisbane), Rev. John Flynn, O.B.E. (Sydney), Professor J. A. Gunn, B.Sc., M.A., Ph.D. (Melbourne), James McRae, M.A. (Malvern, Victoria), Henry Robinson, M.D. (London).

Honorary Secretaries: George Simpson, M.B., M.R.C.P. (Heidelberg Road, Ivanhoe, N.21, Victoria), L. Dougall Callander, M.D. (Danum House, 6A, South Parade, Doncaster).

Programme.

Thursday, September 12.

10 a.m.—Discussion, "Australian Aerial Medical Services", to be opened by Dr. Allan Vickers (Western Australia), followed by Rev. John Flynn. Discussion, "Social Aims of Mental Hygiene", to be opened by Professor Harvey Sutton (Sydney), followed by Professor J. A. Gunn (Melbourne), Dr. R. S. Ellery (Melbourne), Dr. James McRae (Melbourne).

Friday, September 13.

10 a.m. (combined with Section of Public Medicine *et cetera*).—Discussion, "Racial Pressure Problems in Australia and Neighbourhood", to be opened by Sir R. W. Cilento (Brisbane).

The following section will meet on one day:

DERMATOLOGY.

Office-Bearers.

Persident: S. Watson Smith, M.D., F.R.C.P., M.R.C.P. (Bournemouth).

Vice-Presidents: L. P. Johnston, M.B., M.S. (Sydney), Herman Lawrence, M.R.C.P. (Melbourne), J. E. McGlashan, M.C., M.B., B.S. (Perth, Western Australia), W. C. T. Upton, M.B., Ch.M. (Adelaide).

Honorary Secretaries: R. R. Wettenhall, M.B., Ch.B. (85, Spring Street, Melbourne), Alice B. Carleton, M.B., Ch.B. (45, Banbury Road, Oxford).

Programme.

Wednesday, September 11.

10 a.m.—Discussion, "Incidence of Skin Diseases in Australia", to be opened by Dr. Herman Lawrence (Melbourne), followed by Dr. J. E. McGlashan (Perth, Western Australia), Dr. W. C. T. Upton (Adelaide). Discussion, "Staphylococcal Infections of the Skin and their Treatment", to be opened by Dr. J. Ivan Connor (Melbourne). Discussion, "Some Aspects of Mycological Infections and their Treatment", to be opened by Dr. J. C. Belisario (Sydney), followed by Dr. J. Witton Flynn (Sydney).

IRISH MEDICAL SCHOOLS AND GRADUATES' ASSOCIATION LUNCHEON.

The Irish Medical Schools and Graduates' Association luncheon is to be held on Wednesday, September 11, at the Hotel Windsor at 1 p.m. Any interstate visitors (ladies included) who desire to attend this function are asked to notify Dr. W. J. Newing, 55, Collins Street, Melbourne, as soon as possible.

NOMINATIONS AND ELECTIONS.

THE undermentioned has been nominated for election as a member of the New South Wales Branch of the British Medical Association:

Adam, Geoffrey Shedden, M.B., B.S., 1933 (Univ. Sydney), Newcastle Hospital, Newcastle.

Correspondence.

THE HEREDITARY FACTOR IN MENTAL DISORDERS.

SIR: The sub-leader on "Mental Deficiency" in your issue of June 22 opens up very awkward questions indeed in respect of mental disorders in general. I do not refer to the dilemma of the eugenists—though it must appear little short of a human tragedy if the incidence of genetic forms of feeble-mindedness shall be proved to be wholly fortuitous and beyond human control. I refer rather to the plight of the psycho-pathologist and psychiatrist. If there be indeed "little support for the view that heredity plays an important part in the production of mental deficiency", it is difficult to understand how there should be any element at all of "heredity", strictly speaking, in those forms of mental disorder which make their appearance after a period of apparent "normality". And if this be so, these our guides would seem to have seriously misled us. We have not need (we must believe) nor, indeed, any right to look beyond "nurture" and "environment" for the creation of disposing factors that shall determine the incidence of, *exempli gratia*, "shell shock" in a world war or "neurasthenia" in a national "depression", not to speak of the persistence and spread in the national health picture of that shocking smudge—the assorted array of "psychoses". All must be preventible; and, "if preventible, why not prevented". The whole social and medical outlook on the matter of mental disorders seems to me involved.

Or can it be that, though "mental deficiency" in the form that produces "low" and "high grade" defectives is not, or is but slightly, heritable, the constitution that makes some men much more prone than others to break-down under mental strain is ? I should be grateful for guidance in this matter, and quite prepared to be shown up as ignorant. For it is a matter that deeply concerns the public weal both in peace and in war; and, moreover, is one in which the scientific reputation of the medical profession is deeply involved.

Yours, etc.,

A. G. BUTLER.

Melbourne,
July 11, 1935.

THE WORKERS' COMPENSATION ACT AND BUSH NURSES.

Sir: As a matter of interest to medical practitioners in the country, I should be glad if you would publish the following circular, which has been sent to all bush nursing centres:

A person who is injured in the course of his occupation or employment and is thereby disabled for more than seven days is an "Injured Worker" within the meaning of the Act, and is entitled to be compensated.

Such compensation is paid by the Insurance Company with whom the worker has been insured by his employer. The Insurance Company pays also the cost of treatment and of any medical certificates required.

The Insurance Company may dispute the worker's claim for compensation and treatment. Such a case may ultimately come before the Workers' Compensation Commission for decision. If so, the Commission will attach great importance to the medical evidence of the injury and of the treatment given. If medical evidence is lacking or defective, the worker will be prejudiced, even though his claim be perfectly sound.

Bush Nurses are often called on to treat and give certificates about injured workers. For guidance in such cases the following instructions are now issued to all Bush Nurses:

1. In all cases give First Aid as required.
2. In any severe case insist on treatment by a doctor without delay.
3. If the patient's disability continues for more than seven days, so that he becomes an "injured worker" within the meaning of the Act, insist on referring him to a doctor.

   N.B.—The Insurance Company is liable for the expense of treatment.
4. Refuse absolutely to give any certificate of disability or of fitness to resume work.

Yours, etc.,

R. J. Millard,
President, New South Wales Bush Nursing Association.

Sydney,
July 16, 1935.

Obituary.

JOSEPH LOVE.

Dr. Joseph Love, who died, as reported in a previous issue, on June 29, 1935, at his home at East St. Kilda, Melbourne, Victoria, was born at Caernown, County Donegal, Ireland, on August 15, 1884. He came to Australia with his parents when he was five years old. His father was the late Reverend G. C. Love, for many years the Presbyterian minister at Strathalbyn, South Australia, and on several occasions the Moderator of the Presbyterian Church of that State.

Joseph Love was educated at Prince Alfred College, Adelaide, and later at Scotch College, Melbourne. He entered upon his medical course at Melbourne University in 1902 and was a resident student at Ormond College throughout his course. He obtained his qualifying degrees in 1907. His contemporaries will remember him well for his rowing prowess. He rowed for Scotch College in the first eight-oared public school boat race and afterwards was captain of the boats at Ormond College and for six consecutive years rowed in the winning inter-collegiate crew.

His post-graduate career opened in Tasmania. He was a resident medical officer for two years at the Hobart General Hospital and for the next seven years was surgeon to the Mount Lyell Mine and Queenstown Hospital. He left this work in 1917 for war service in France and Belgium with the rank of Captain in the Australian Army Medical Corps and was on duty as embarkation medical officer until 1919. Before returning to Australia he did post-graduate work in London, where he was associated with Sir Thomas Dunhill.

After the war he came to East St. Kilda, became a busy suburban general practitioner and devoted special attention to surgery. His enthusiasm for surgery was so great that he achieved the very difficult feat of working for and obtaining the degree of Master of Surgery of Melbourne without relinquishing his practice. At this time he joined the honorary staff at the Alfred Hospital and occupied the post of emergency surgeon until he relinquished it last year on account of ill-health. For many years he had been a surgeon in the Venereal Diseases Clinic at the Alfred Hospital and he retained this position to the end. He was a Fellow of the Royal Australasian College of Surgeons.

Latterly he was seeing fewer patients at his home and many more in his consultative practice at 71, Collins Street. He was a keen student and contributed several useful papers on carbon monoxide poisoning, quantitative Wassermann reactions and psittacosis to the *Australian Medical Journal* and The Medical Journal of Australia, and frequently took part in discussions at scientific meetings. He was a delightful companion with a whimsical sense of humour, and thoroughly enjoyed a game of golf or fly-fishing expeditions along country streams.

We extend our sympathy to his widow and to his sons, the elder of whom is a fourth-year medical student at Ormond College; the younger is still at Scotch College.

Dr. M. D. Silberberg writes:

The genial personality of the late Dr. Joseph Love will long remain as a happy memory to a large circle of friends. Those who knew him from the time of his undergraduate days realize that he never departed from the high ideals of life and work then formed. Few men maintained as uniformly as he did a persistent broad-minded tolerance and cheerfulness, and also courage which did not desert him, even when he knew that a succession of vascular lesions assailed him.

Hard work he sought, and gloried in it. Perhaps no more arduous place for general practice could be found than the mining district of Zeehan, on the west coast of Tasmania, some twenty-five years ago. Here the bush is trackless and the rainfall is measured in feet.

Many interesting stories and sidelights of practice he told of those early days, and he related them well, being an excellent raconteur. The strenuous work of those times, followed by war service, and then even more so the unremitting toil of recent years, no doubt undermined his health and led to vascular disorders at a comparatively early age.

Whilst in the midst of a large and busy general practice he spurred himself to study for the M.S. (Melbourne) degree and attained this difficult distinction. This stands out as a notable feat of sustained mental effort only rarely achieved by others similarly placed. His ambition was to develop a surgical practice and he did not spare himself in the endeavour. In addition to carrying on his busy practice he was emergency surgeon to the Alfred Hospital, which meant many hours in the operating theatre, mostly in the weary night. To every case he gave earnest thought in regard to pre-operative diagnosis and the best surgical procedure to be adopted. Not only this; he also worked in the venereal diseases clinic and in the surgical out-patient department.

Perhaps his undergraduate success as an oarsman gave him undue confidence in his powers of endurance. He represented Ormond College and the University in many a winning crew.

His colleagues of the Alfred Hospital will miss his cheery smile, and so will a large circle of friends and patients. Our heartfelt sympathy goes out to his bereaved widow and two sons.

Dr. Albert Weigall writes:

I have known Joseph Love for over thirty-five years, and for the past ten or twelve years as a near neighbour. His outstanding characteristics were his philanthropy and his unfailing geniality.

In my work I placed much reliance on him in difficult cases, for not only was he a sound and conservative surgeon, but also I found his opinion in medical cases most helpful and illuminating. His eagerness to help the sick was, if anything, intensified by their poverty.

Having had the privilege of attending him in his last illness, I was deeply impressed by his cheerful resignation to restrictions that must have been most irksome to a man that loved his work and play as he did. While medical men are reputed to be bad patients, he was one of my best and went out of his life as he lived it—thinking first of others.

RODERICK AITCHISON.

WE regret to announce the death of Dr. Roderick Aitchison, which occurred at Brighton, Victoria, on July 24, 1935.

PATRICK JOHN COLLINS.

WE regret to announce the death of Dr. Patrick John Collins, which occurred at Woollahra, New South Wales, on July 28, 1935.

Analytical Department.

"PROTOMIN."

"PROTOMIN" is a product of the Kelvin Chemical Company, of 163, Pitt Street, Sydney. It is put up in tablet form and contains what is claimed to be a stable form of ferrous chloride. In support of this claim the manufacturers have forwarded a report from their analyst, which is as follows:

> I received a bottle of your Protomin tablets with instructions to examine for ferrous iron content at fortnightly intervals after opening.
>
> The bottle was corked and returned to the container after the removal of the tablets for analysis.
>
> No other precautions were taken to keep from oxidation.

Date.		Ferrous Iron per Tablet.
7.2.35	..	0·037 gramme
21.2.35	..	0·038 gramme
7.3.35	..	0·038 gramme
21.3.35	..	0·038 gramme

> The ferrous iron content of several tablets was averaged at each determination.

A sample of "Protomin" was submitted to our analysts. They found that the average weight of the tablets was 0·213 gramme; the ferrous iron in each tablet was 0·0388 gramme; the ferric iron in each tablet was 0·0019 gramme. The amount of ferrous iron present corresponded to 2·13 grains for ferrous chloride ($FeCl_2.4H_2O$) per tablet. After an interval of three weeks a further analysis was made. During this time the tablets were kept in the original bottle, and, apart from keeping the bottle corked, no precautions against oxidation were taken. The average weight of the tablets was 0·213 gramme; the ferrous iron in each tablet was 0·0389 gramme and the amount of ferric iron in each tablet was 0·0019 gramme. We concur in the opinion of our analysts that under normal conditions there will be no significant amount of oxidation of the ferrous iron in the tablets.

"Protomin" tablets may be recommended as a suitable medicament for use in the types of anæmia that are amenable to ferrous iron therapy.

THE ARCHIBALD WATSON PRIZE FUND.

THE jubilee of the medical school of the University of Adelaide will be celebrated at the end of August, 1936.

Professor Watson is the only surviving member of the staff which was appointed at the foundation of the school fifty years ago. It has seemed fitting that those who owe so much to Professor Watson's teaching should mark the occasion by subscribing towards the foundation in his honour of an Archibald Watson Prize in Anatomy. It has therefore been decided to ask each of those who studied anatomy during Professor Watson's term of office to subscribe one guinea or more with that object. It is believed that there are others in Australia whose indebtedness to Professor Watson will doubtless prompt them to subscribe.

Each subscriber of one guinea or more will be entitled to a coloured reproduction of McInnes's admirable portrait of Professor Watson, which was hung in the new building of the Royal Australasian College of Surgeons on the occasion of its opening last March.

Subscriptions should be forwarded to:

Mr. Julian Smith, senior, 59, Collins Street, Melbourne, C.1;
Dr. T. Ambrose, 256, St. George's Terrace, Perth;
Sir Raphael Cilento, Department of Health, Brisbane;
Dr. J. L. T. Isbister, 185, Macquarie Street, Sydney;
Dr. A. M. Cudmore, 188, North Terrace, Adelaide;
Dr. Frank S. Hone, 178 North Terrace, Adelaide;
Dr. Bronte Smeaton, 197, North Terrace, Adelaide;

or to the Secretaries:

Dr. I. B. Jose, 188, North Terrace, Adelaide;
Sir Henry Newland, 163, North Terrace, Adelaide.

THE STAWELL MEMORIAL FUND.

THE undermentioned subscriptions have been received for the Stawell Memorial Fund:

£10 10s.: Dr. J. H. Shaw.
£5 5s.: Dr. W. E. Wilson, Dr. H. J. Gray, Dr. K. Hiller, Dr. W. W. S. Johnston, Dr. J. R. Bell.
£2 2s.: Dr. G. Weigall, Dr. J. P. Ainslie, Dr. C. Ellis.
£1 1s.: Dr. J. E. Nihill, Dr. W. J. Craig, Dr. R. H. Strong.

THE GEORGE MACDONALD TESTIMONIAL FUND.

THE undermentioned subscription has been received for the George Macdonald Testimonial Fund:

£1 1s.: Dr. H. B. Little.

NOTICE.

THE Honorary Secretary of the Royal Australasian College of Surgeons announces that a lecture will be delivered by Dr. Alan Newton at the College building, Spring Street, Melbourne, on Friday, August 16, 1935, at 8.15 o'clock p.m. This lecture, which will be entitled "Major Surgery in Patients over Seventy Years of Age", will inaugurate a series to be delivered at the headquarters of the College. All members of the medical profession are invited to attend.

Books Received.

POCKET MONOGRAPHS ON PRACTICAL MEDICINE: OPHTHALMOLOGY IN GENERAL PRACTICE, by O. G. Morgan; 1935. London: John Bale, Sons and Danielsson, Limited. Foolscap 8vo., pp. 57, with illustrations. Price: 2s. 6d. net.

EPIDEMICS AND CROWD-DISEASES: AN INTRODUCTION TO THE STUDY OF EPIDEMIOLOGY, by Major Greenwood, D.Sc., F.R.C.P., F.R.S.; 1935. London: Williams and Norgate, Limited. Demy 8vo., pp. 409. Price: 21s. net.

Diary for the Month.

AUG. 5.—New South Wales Branch, B.M.A.: Organization and Science Committee.
AUG. 6.—Tasmanian Branch, B.M.A.: Council.
AUG. 7.—Victorian Branch, B.M.A.: Branch.
AUG. 7.—Western Australian Branch, B.M.A.: Council.
AUG. 9.—Queensland Branch, B.M.A.: Council.
AUG. 13.—Tasmanian Branch, B.M.A.: Branch.
AUG. 13.—New South Wales Branch, B.M.A.: Executive and Finance Committee.
AUG. 20.—New South Wales Branch, B.M.A.: Ethics Committee.
AUG. 20.—Tasmanian Branch, B.M.A.: Council.
AUG. 21.—Western Australian Branch, B.M.A.: Branch.
AUG. 21.—Victorian Branch, B.M.A.: Clinical Meeting.
AUG. 22.—New South Wales Branch, B.M.A.: Clinical Meeting.
AUG. 23.—Queensland Branch, B.M.A.: Council.
AUG. 27.—New South Wales Branch, B.M.A.: Medical Politics Committee.
AUG. 28.—Victorian Branch, B.M.A.: Council.
AUG. 29.—South Australian Branch, B.M.A.: Branch.
AUG. 29.—New South Wales Branch, B.M.A.: Branch.

Medical Appointments.

Dr. M. Mandelstam (B.M.A.) has been appointed Medical Officer of Health by the Augusta-Margaret River Road Board, Western Australia.

* * *

Dr. John Halliday (B.M.A.) has been temporarily appointed a Member of the Boards of Official Visitors to the Mental Hospitals at Parramatta and Rydalmere, New South Wales.

* * *

Dr. A. S. Walker (B.M.A.) has been appointed a Member of the Board to Control the Campaign against Tuberculosis in New South Wales.

* * *

Dr. E. S. Morris (B.M.A.) has been appointed a Member of the Building Regulation Advisory Committee, New South Wales.

* * *

Dr. T. R. Gaha has been appointed a Member of the Board of Optical Registration, Tasmania, pursuant to the provisions of the *Opticians Act*, 1913.

* * *

Dr. F. M. Read (B.M.A.) has been appointed, pursuant to the provisions of the *Workers' Compensation Act*, 1928, a Certifying Medical Practitioner and Medical Referee at Canterbury, Victoria.

Medical Appointments Vacant, etc.

For announcements of medical appointments vacant, assistants, *locum tenentes* sought, etc., see "Advertiser", pages xvi-xviii.

COMMONWEALTH OF AUSTRALIA: Medical Officer.
KALGOORLIE DISTRICT HOSPITAL, KALGOORLIE, WESTERN AUSTRALIA: Resident Medical Officer.
LAUNCESTON PUBLIC HOSPITAL, LAUNCESTON, TASMANIA: Resident Medical Officer.

Medical Appointments: Important Notice.

MEDICAL practitioners are requested not to apply for any appointment referred to in the following table without having first communicated with the Honorary Secretary of the Branch named in the first column, or with the Medical Secretary of the British Medical Association, Tavistock Square, London, W.C.1.

BRANCH.	APPOINTMENTS.
NEW SOUTH WALES: Honorary Secretary, 135, Macquarie Street, Sydney.	Australian Natives' Association. Ashfield and District United Friendly Societies' Dispensary. Balmain United Friendly Societies' Dispensary. Friendly Society Lodges at Casino. Leichhardt and Petersham United Friendly Societies' Dispensary. Manchester Unity Medical and Dispensing Institute, Oxford Street, Sydney. North Sydney Friendly Societies' Dispensary Limited. People's Prudential Assurance Company Limited. Phœnix Mutual Provident Society.
VICTORIAN: Honorary Secretary, Medical Society Hall, East Melbourne.	All Institutes or Medical Dispensaries. Australian Prudential Association, Proprietary, Limited. Mutual National Provident Club. National Provident Association. Hospital or other appointments outside Victoria.
QUEENSLAND: Honorary Secretary, B.M.A. Building, Adelaide Street, Brisbane.	Brisbane Associate Friendly Societies' Medical Institute. Chillagoe Hospital. Members accepting LODGE appointment and those desiring to accept appointments to any COUNTRY HOSPITAL are advised, in their own interests, to submit a copy of their Agreement to the Council before signing.
SOUTH AUSTRALIAN: Secretary, 207, North Terrace, Adelaide.	Officer of Health, District Council of Elliston. All Lodge Appointments in South Australia. All Contract Practice Appointments in South Australia.
WESTERN AUSTRALIAN: Honorary Secretary, 205, Saint George's Terrace, Perth.	All Contract Practice Appointments in Western Australia.
NEW ZEALAND (Wellington Division): Honorary Secretary, Wellington.	Friendly Society Lodges, Wellington, New Zealand.

Editorial Notices.

MANUSCRIPTS forwarded to the office of this journal cannot under any circumstances be returned. Original articles forwarded for publication are understood to be offered to THE MEDICAL JOURNAL OF AUSTRALIA alone, unless the contrary be stated.

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Members and subscribers are requested to notify the Manager, THE MEDICAL JOURNAL OF AUSTRALIA, Seamer Street, Glebe, New South Wales, without delay, of any irregularity in the delivery of this journal. The management cannot accept any responsibility or recognise any claim arising out of non-receipt of journals unless such a notification is received within one month.

SUBSCRIPTION RATES.—Medical students and others not receiving THE MEDICAL JOURNAL OF AUSTRALIA in virtue of membership of the Branches of the British Medical Association in the Commonwealth can become subscribers to the journal by applying to the Manager or through the usual agents and booksellers. Subscriptions can commence at the beginning of any quarter and are renewable on December 31. The rates are £1 for Australia and £2 5s. abroad *per annum* payable in advance.